ornl

ORNL/RAP-38

#2086

OAK RIDGE NATIONAL LABORATORY

MARTIN MARIETTA

# Evaluation of Human Health Risks from Mixtures of Hazardous Chemicals and Radionuclides

T. D. Jones
B. A. Owen
S. M. Wells



MANAGED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE UNITED STATES
DEPARTMENT OF ENERGY

#2086

ORNL/RAP-38

# EVALUATION OF HUMAN HEALTH RISKS FROM MIXTURES OF HAZARDOUS CHEMICALS AND RADIONUCLIDES*

T. D. Jones
B. A. Owen
S. M. Wells

September 1987

PREPARED BY THE
OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE 37831
OPERATED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE
U.S. DEPARTMENT OF ENERGY
UNDER
Contract No. DE-AC05-84OR21400

---

*Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

## PREFACE

This report was prepared by staff members of the Health and Safety Research Division (HASRD) in support of the Remedial Action Program (RAP) for the Oak Ridge Site. Described is a summary of progress achieved from October 1986 through September 1987. As additional tasks are completed, it is expected that the present report will serve as a functional infrastructure for a final ORNL report and journal article on "Evaluation of Human Health Risks from Mixtures of Hazardous Chemicals and Radionuclides." In addition, various subtasks will be submitted for peer review and journal publication.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

## EXECUTIVE SUMMARY

The primary goal of this study is to develop a risk-based common scale for consideration of radionuclides, carcinogenic chemicals, and noncarcinogenic chemicals according to the logic illustrated in Fig. 1. The common scale is needed as a basis for management of waste products and control of environmental pollutants. Also, prioritization of various remedial actions and decisions based on cost vs benefit and acceptable, unacceptable, voluntary, and involuntary exposures cannot be made on a sound technical basis unless different harmful agents can be compared, with a high degree of relative accuracy, on a common scale that either explicitly or implicitly indexes potential detriment to human health.

It is frequently recognized that environmental pollutants comprised of mixtures of radionuclides, chemicals classified as carcinogens, and chemicals classified as noncarcinogens may act in combination to amplify the etiological development of specific pathological diseases. Current risk analogies do not have the flexibility to adjust for a unifying hypothesis for the potentiating effect from one toxic agent working to amplify the preclinical lesions initiated by a different toxic agent. The goal of this study, viz. a risk-based common scale, attempts to make a first step towards satisfying this complex need.

The processes by which hazardous insults act in combination to amplify or impede disease processes are not adequately understood at this time. Specific experimental designs may demonstrate synergism, and other experimental designs may demonstrate antagonism of disease processes. Thus, analyses of the effects from individual chemicals (or insults) may or may not be useful in assessing the cumulative effect from multiple stressors. The method described in this paper serves as a useful "strawman" in that the effects of chemicals tested individually may be compared with the effects from a complex mixture. These comparisons should provide useful insight as to the testing and regulation of complex mixtures.

Regulatory criteria are highly kinetic in that individual chemicals are constantly being reclassified according to "weight of evidence" as to whether specific chemicals are carcinogenic to animals, carcinogenic to man, or "potential carcinogens." In addition to reclassification, the Environmental Protection Agency (EPA) subjectively defines action levels independently for different chemical classes and for different activities. For example, an action level of only one additional cancer per million persons exposed was promulgated for land disposal considerations, but the action level is 10- or 100-fold higher for the contaminants in drinking water.

EPA regulatory science is founded on absolute decision making where the magnitude of a particular hazardous agent is analyzed without the advantage of relative comparisons with other hazardous agents. Thus, EPA has regulated radiochemicals, carcinogenic chemicals, and noncarcinogenic chemicals separately and independently, and the *Superfund Public Health Evaluation Manual* declares that "Indicator scores for carcinogens and noncarcinogens are not on comparable scales and should never be compared."

EPA's methodology of promulgating criteria commonly involves selecting human or animal test data to be analyzed, investigating the dose response, incorporating margins of safety, scaling treatment dose from the test species to man, scaling the response from the test species to man, and setting an action level for "acceptable risk."

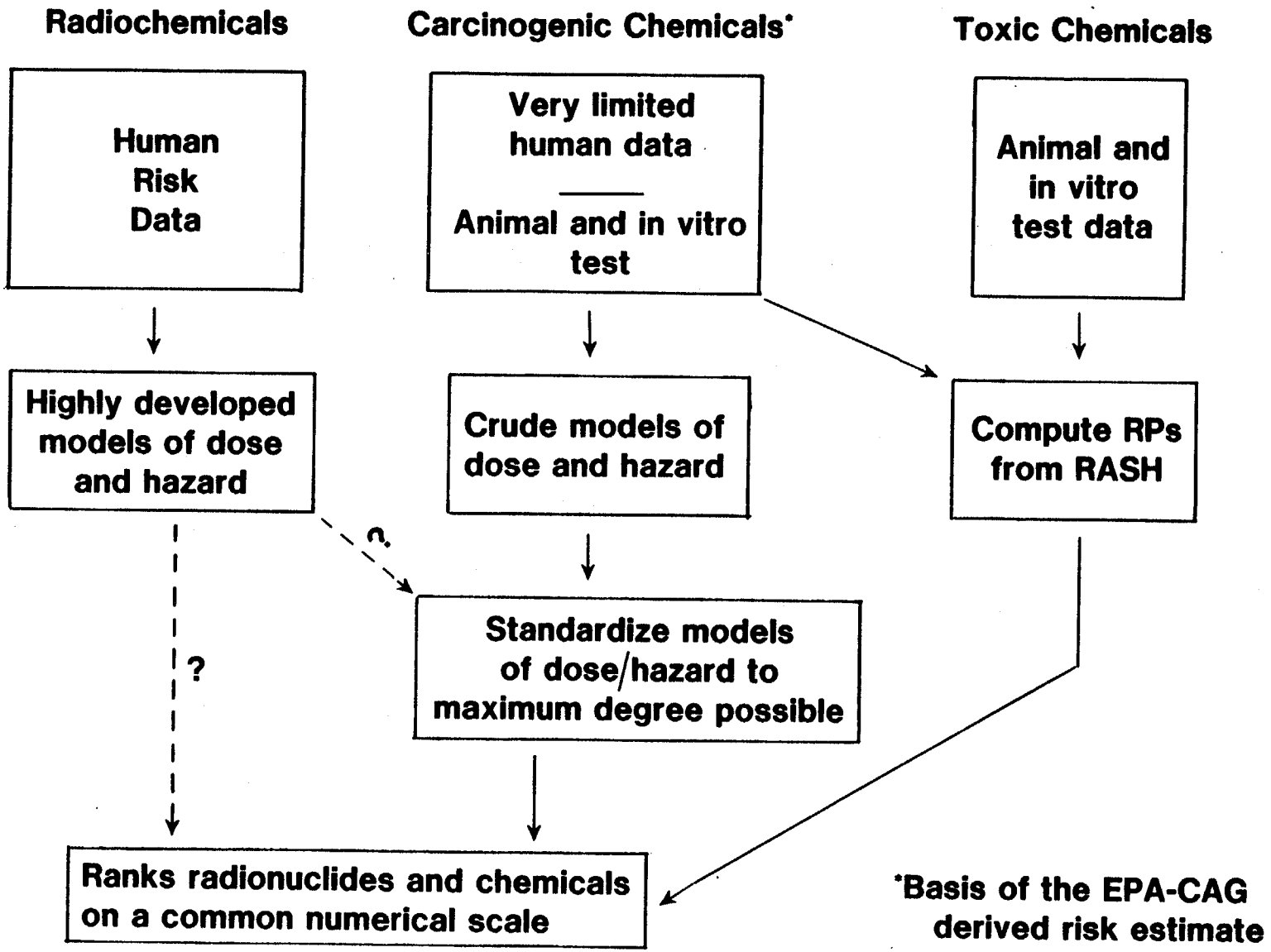



Fig. 1. RASH analysis for mixed wastes.

The EPA process typically is based on only one toxicological or epidemiological study. If reliable human data are available (as for chromium), then EPA models can be realistic. The EPA policy is to err towards safety when faced with data gaps. In these situations the EPA chooses to use safety factors and extreme conditions instead of relying on data-intensive relative comparisons.

Chemicals such as PCBs are regulated using EPA levels widely believed to be safe, but the EPA models that are believed to be highly protective of human health become quite unrealistic in the absence of reliable human data. Thus, no relative accuracy is found across criteria for various hazardous pollutants, and the ranking of the risks posed by different chemicals becomes scrambled. Additional discussion is given to describe why this study selectively chooses limited methods from the EPA regulatory models.

An important subtask of this study is to "sort out" the EPA models that are realistic in an absolute sense (they are a subset developed from epidemiologically based data) and to mate those models with more accurate relative comparisons so that an improved realistic risk-based common scale can be defined for those individual chemicals and complex mixtures that lack sufficient data for a realistic evaluation of absolute risk. This new risk-based scale attempts to preserve the accurate relative ranking of individual chemicals, even those chemicals with major data gaps.

A rapid screening of hazard (RASH) methodology has been developed and published (Jones et al. 1985; Jones et al. 1987) for relative comparisons of toxicological potency based on *in vitro* and *in vivo* test data published in the *Registry of Toxic Effects of Chemical Substances* (RTECS) (Lewis and Sweet 1983-1984). The RASH methodology is based on the evidence that exposure to any agent that stimulates compensatory cell proliferation above the normal homeostatic level can act to potentiate carcinogenesis in humans exposed simultaneously or serially to agents that contribute to toxicity (Jones et al. 1983; Jones 1985).

Radionuclides have been evaluated and managed according to dosimetry and mathematical risk analogies that are developed in adequate detail (ICRP 1980) so that one significant exposure experience to a human population (such as the Japanese atomic bomb survivors) can be evaluated. The mathematical models can then be reevaluated for different exposure conditions to predict the magnitude of the hazard for a hypothetical human population subjected to an entirely different source of radiation and/or treatment schedule. The biophysical and radiobiological models are quite realistic in contrast to models for toxic chemicals. For example, radiological models consider absorption efficiency factors for various compounds and follow the metabolism, distribution, and retention within the fluids, organs, and cells of the body.

Bioassays published in RTECS have not been conducted for radionuclides; thus, it is obligatory to put the unitless relative potency ranking of chemicals derived from the RASH analysis on a realistic risk-equivalent basis so that radionuclides and chemical hazards can be compared directly. The RASH method evaluates all chemicals independent of designation by expert committee as to whether weight of evidence indicates a chemical is a "carcinogen" or a "noncarcinogen."

In support of this need, absorption coefficients for the chemicals identified as potential pollutants on the ORNL site have been developed (see Appendix E), and the bridge or common scale component of this analysis is shown in Fig. 1 and labeled as "Standardize models of dose/hazard to maximum degree possible."

Thirteen radionuclides, eight toxic chemicals, and six chemical carcinogens have been previously identified as potential contaminants at various sites associated with ORNL. This reporting considers those 26 pollutants in the level of detail adequate to illustrate a risk-based common scale.

Because this study is based on a realistic assessment of risk and employs actual doses or concentrations in the tissues of the human body, results are useful for environmental pathways analyses and soil contamination criteria. Thus, an important component of this study is to collaborate with other members of the remedial action program (RAP) study team.

At this reporting, all aspects of the risk-based common scale have been developed adequately except for the standardization of dose and risk module of Fig. 1, evaluation of additional pollutants currently listed in the ORNL inventory, and final coordination of intermodule communication of tasks described by boxes in Fig. 1.

EPA regulatory science is "model intensive" and "data sparse." In contrast, the intent of the methodology proposed in this study is to be "data intensive" and "model sparse." Because EPA's action levels such as $10^{-5}$ per person-lifetime are mathematical analogies with implicitly wide and chemical-specific margins of safety, it is not known whether "true" risk to an exposed population would be in agreement with risk models, near zero, or somewhere between. In addition, some individuals argue unrealistically for a risk-free environment. More realistically, most individuals recognize a need to balance resources and implicitly accept a *de minimis* policy that ignores insignificant matters. Repeatedly the EPA has declared a policy of not regulating an undemonstrated hazard, but it continues to use linear extrapolation models to predict risk levels thought to derive from near zero-level concentrations.

To aid in these and similar decisions, it seems desirable to offer an alternative to a crudely calculated action level such as $10^{-5}$ per person-lifetime. Two such alternatives are offered in this report. One alternative is to make accurate relative comparisons between toxic chemicals in drinking water and the benzo(*a*)pyrene content of common foods. A second standard for comparison is to make accurate relative comparisons between toxic chemicals in drinking water and breakdown products such as trihalomethanes resulting from water chlorination. Because water chlorination clearly benefits human health in contrast to undesirably polluted water, a screening decision, or action level, could be set at some fraction of the toxicity deriving from chlorination of public drinking water.

This report draws heavily from regulatory sciences, biological test results, risk analysis, radiation dosimetry, etc. As a result, this report reflects a spectrum of terms drawn from many disciplines. Because some readers may be unfamiliar with certain technical terms, a glossary is included at the end of this summary.

# GLOSSARY

*absolute*: the traditional method of decision making used by the EPA, characterized by reliance upon expert committees who utilize model-intensive, data-sparse exposure scenarios bolstered by large safety factors to evaluate human health effects.

*absorption coefficient*: an efficiency factor used to approximate the fraction of the exposure absorbed into the circulating fluids of the body. Absorption coefficients are used for ingestion, inhalation, and dermal exposures.

*acceptable risk*: Mathematical models are used to calculate the potential level of damage in a human population. Currently, if less than one person is expected to be injured pathologically from a population of 100,000 or more, this may be taken as an "acceptable" level of risk, viz. $10^{-5}$ per person-lifetime.

*animal slopes*: The CAG uses a multistage model to fit experimental data from dose-response studies. Animal slopes refer to the linearity of the multistage model at low dose.

*ATSDR*: Agency for Toxic Substances and Disease Registry.

*bioassay*: an *in vitro* or *in vivo* test used to measure the effect of a chemical or physical agent.

*CAG*: The Carcinogen Assessment Group of EPA.

*CAG risk coefficient*: a constant that, when multiplied by dose, describes a level of risk. The CAG publications usually call this value the "animal slope" or simply "slope." Units of the slope are typically given in $(mg/kg/day)^{-1}$.

*carcinogenic chemicals*: usually a reference to chemicals listed as "known," "suspected," and "potential" carcinogens. The carcinogenic chemicals are typically those listed by the IARC.

*carcinogenicity*: the capacity to cause, enhance, or potentiate cancer.

*carcinoma*: a malignant tumor derived from epithelial tissue.

*CERCLA*: the Comprehensive Environmental Response, Compensation, and Liability Act of 1980. It established the Superfund.

*closure*: the operational and legal shutdown of an activity.

*criteria*: a legal limit that should not be exceeded. In the absence of regulatory criteria, an estimate derived by a nonofficial source for management and storage of hazardous waste.

*data gaps*: insufficiencies or inadequacies in toxicological data required to accurately assess health effects; usually compensated for by incorporation of large safety factors in risk calculations.

*data intensive*: a characteristic of an analysis designed to maximize the use of experimental data to evaluate an effect.

*data sparse*: the use of a small amount of data and a strong reliance on mathematical models to evaluate an effect.

*decision point*: a calculated or measured value that changes the course of action from what would be taken at a lower value.

*dosimetry*: the measurement of dose or dose-related quantities.

*DWPL*: Drinking Water Priority List, as mandated by the SDWA; a list of priority contaminants found in public water systems that have documented or suspected adverse health impacts.

*$ED_{10}$*: the estimated dose associated with a lifetime excess cancer risk of 10%, the reciprocal of which is called the RQ potency factor and is used (with weight-of-evidence) in relative ranking of Superfund site chemicals.

*EPA Water*: this refers to EPA Water Quality Criteria activities.

*expert committees*: multidisciplinary groups of experts charged by an authoritative body such as EPA, NIOSH, etc., to evaluate a particular hazard or risk.

*Group A*: a human carcinogen based upon sufficient epidemiological evidence.

*Group B1*: a probable human carcinogen based upon limited epidemiological evidence.

*Group B2*: a probable human carcinogen based upon sufficient evidence of carcinogenicity in animals but inadequate evidence in humans.

*Group C*: a possible human carcinogen based upon limited evidence of carcinogenicity in animals.

*Group D*: not classified because of inadequate evidence of carcinogenicity in animals.

*Group E*: no evidence of carcinogenicity in humans in at least two adequate animal tests or in both epidemiologic and animal studies.

*hazard*: a calculation or measurement of potential harm. Does not imply that the effect or harm will actually occur; typically an overestimate of actual outcome or risk.

*Hazard Ranking System*: a screening tool for assigning sites to the National Priorities List (NPL) wherein a numerical score is derived to reflect

the potential for harm to humans or the environment from migration of hazardous substances by groundwater, surface water, or air routes.

*hazardous chemicals*: refers, in this report, to all chemicals. Harm can be induced by any chemical at some concentration. Even pure oxygen and distilled water are toxic at high concentrations. This usage is not consistent with EPA's use of the term.

*HRS*: see Hazard Ranking System.

*human slopes*: a term used by CAG to indicate a linear dose response fitted to human data. The multistage model was not used when CAG analyzed human data.

*hyperplastic nodule*: a precancerous response to tissue trauma characterized by cellular proliferation and increase in size and weight of the affected organ.

*IARC*: International Agency for Research on Cancer.

*infant regulation*: a guidance value derived early in the regulatory history of a particular chemical. Infant regulations are subject to sudden and potentially large changes.

*initiate*: to induce a precarcinogenic lesion or condition by administering a subeffective dose of a carcinogen.

*interviewing chemical*: a term used in a descriptive sense to denote a chemical being assayed for toxicology potency. That chemical may or may not be produced or used for industrial processes, depending upon its toxicity.

*linearized multistage*: see slopes.

*LOAEL*: lowest-observed-adverse-effect level

*mature regulation*: a guidance value derived from a large amount of test data or actual human experience.

*maximum tolerated dose (MTD)*: this is usually taken at two- or four-fold less than a dose that produces frank lesions of acute toxicity. The magnitude of the MTD is determined by experimental design and duration of treatment.

*MCL*: maximum contaminant levels; enforceable standards set by the EPA under amendments to the SDWA in 1986; should be set as close to the MCLG as practically feasible.

*MCLG*: maximum contaminant level goal; non-enforceable health goals set at a level of no known or anticipated adverse health effects with an adequate margin of safety.

*model intensive*: reliance upon mathematical models moreso than upon experimental data to evaluate human health effects.

*National Priorities List*: a list of sites that qualify for Superfund-financed remedial action on the basis of their HRS score (above 28.5).

*NOAEL*: no-observed-adverse-effect level.

*noncarcinogen*: generally, a treatment not expected to cause or potentiate carcinogenesis. Thus, the intrinsic characteristics of the treatment, the characteristics of the test model, and the conditions of exposure determine whether a treatment is a carcinogen or a noncarcinogen.

*NPL*: see National Priorities List.

*PCBs*: polychlorinated biphenyls.

*permissible*: an exposure concentration or treatment not expected to cause an unacceptable level of hazard of risk.

*potentiate*: to enhance a pre-established carcinogenic activity.

*promote*: to establish carcinogenesis through chemical or physical means applied in conjunction with an initiator.

*RAC*: see reference air concentration.

*radiochemical*: a toxic chemical that contributes to toxicity predominantly through production of ionizing radiations.

*RASH*: the rapid screening of hazard chemical scoring method (*Toxicological and Industrial Health* 1(4), 1985).

*reference air concentration*: for noncarcinogens, a threshold dose below which health is protected; derived from oral RfDs.

*reference chemical*: a well-studied chemical that serves as a standard for comparison with a chemical about which much less is known.

*reference standard*: a term used to imply the most authoritative epidemiologically based standard. In this document it is proposed that the most authoritative standard may be a composite of risk-based experiences that may serve to dampen the effect of undesirable confounding factors.

*relative*: a newer supplemental method of decision making characterized by minimized reliance upon mathematical models and more data-intensive multipotency comparisons between various biological tests.

*relative potency*: the capacity of a chemical to produce a specified effect relative to the capacity of a standard chemical to produce the same effect. For equal response, relative potency = $D_S/D_T$, where $D_S$ is the dose of the standard chemical and $D_T$ is the dose of the test chemical.

*reportable quantity*: an amount of a pollutant such that a spill in excess of that amount must be reported to EPA.

*RfD*: reference dose.

*risk*: actual harm to a population in contrast to an estimate of the potential hazard.

*risk-equivalent*: the use of a specific level of risk to compare the potency of different pollutants.

*Risk-specific dose*: a term used by EPA to designate the permissible concentration of a carcinogen.

*RMCL*: recommended maximum contaminant level, renamed maximum contaminant level goal (MCLG) under amendments to the SDWA in 1986.

*RP*: relative potency.

*RQ*: see reportable quantity.

*RSD*: see risk specific dose.

*safety factors*: factors used to adjust the NOAEL, NOEL, or LOAEL reported for small experimental test populations to estimate the comparable NOAEL for chronic exposure to larger populations that may contain sensitive subgroups in calculations of ADI; generally used to provide a measure of protection in compensation for data gaps.

*SAR*: structure activity relation that is an evaluation of a chemical based on its chemical structure.

*SARA*: Superfund Amendments and Reauthorization Act of 1986, which sets schedules to be met in conduct of preliminary assessments and site inspections (for data collection) and also mandates improvements to be made in the HRS methodology.

*Sax Index*: a scheme of rating toxicity on a scale of 0 to 3 that is used in combination with a persistence score in evaluating waste characteristics in the HRS methodology; chronic toxicity is not addressed, which is a weakness in the index.

*SDWA*: Safe Drinking Water Act of 1974, which required the EPA to establish national interim primary drinking water regulations applying to public drinking water systems and specifying contaminants that may have any adverse health effects.

*slopes*: see animal slopes and human slopes.

*Test chemical*: similar to an interviewing chemical except that the emphasis is on test results from bioassays instead of on the industrial usage of a chemical or chemical process.

*uncertainty factors*: factors that represent measurable estimates of experimental variability; sometimes incorrectly referred to as safety factors.

*unit risk estimates*: a term used by CAG to indicate a potential excess lifetime risk associated with breathing 1 $\mu g/m^3$ over a 70-year lifespan for a 70-kg person. The quantity is inaccurately named because the estimate is for hazard (not risk), and the unit designates concentration, not "unit risk."

*weight of evidence*: the overall strength of the data indicating the potential carcinogenicity of an agent, categorized into groups A through E.

# 1. GOAL

The primary goal of this study is to develop a risk-based common scale for radionuclides, carcinogenic chemicals, and noncarcinogenic chemicals. The common scale is needed as a basis for management of waste products and control of environmental pollutants. Also, prioritization of various remedial actions and decisions based on acceptable, unacceptable, voluntary, and involuntary exposures cannot be made on a sound technical basis unless different harmful agents can be compared, with a high degree of relative accuracy, on a common scale that either explicitly or implicitly reflects potential detriment to human health. The risk-based methodology proposed in this report depends upon the point of fact that designation as "noncarcinogen" is tentative, based on the subjective decision as to how a particular expert committee evaluates the weight of evidence for a particular chemical. Obviously, the weight of evidence changes with time. Also, "carcinogenic" or "noncarcinogenic" is a classification that depends upon the interaction of a hazardous agent with a biological test model under a particular exposure protocol. Variations in the nature of the hazardous agent, the biological traits of the model, or the parameters of exposure can shift the classification--even for widely tested and monitored carcinogens.

## 2. INTRODUCTION: NEED FOR AN ANALYSIS OF RELATIVE TOXICITIES

Historically, radionuclides, carcinogenic chemicals, and toxic chemicals have been separated into three conceptually distinct classes. According to the *Superfund Public Health Evaluation Manual* (EPA 540/1-86/060), "Carcinogens and noncarcinogens are not on comparable scales and should never be compared." Thus, hazard/risk evaluation and hazard management (including regulatory) practices have been implemented that are unique to each of the three classes. The distinction between hazard to human health and risk of harm to human health is not clear from dictionary definitions. Hazard usually implies a chance happening--an accident or a possible source of danger where the element of probability is emphasized. Risk is possibility of suffering harm or loss--danger or a factor, course, or element involving uncertain danger; hazard (Webster's II: New Riverside University Dictionary 1984). Although these descriptions seem circuitous, with the only obvious distinction being that of "probability" vs "possibility," the EPA has specified that

> "Risk assessment is comprised of the following components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. . . . Hazard identification is the qualitative risk assessment dealing with the inherent toxicity of a chemical substance" (51FR34007).[1]

The traditional approach to hazard evaluation and management is to consider each hazardous chemical or agent individually, without benefit of previous evaluations of other toxic agents, and to limit human exposures to that insult to levels that are judged or calculated to have an insignificant or acceptable impact on human health. Thus, action levels or goals have been set independently for each of the three classes of health hazard considered here. Selected examples of decision/action levels have included: *National Primary Drinking Water Regulations for Radionuclides (51FR34836) "de minimis"* and "as low as reasonably achievable" (ALARA) concepts for ionizing radiations; National Interim Primary Drinking Water Regulations (40FR59566); the analytical limit of chemical detection in food and drug products; and a concentration calculated to cause no more than one premature death in a population of 100,000 persons at lifetime risk from environmental contaminants (Sittig 1980).

Analytical and quantitative chemistry have developed to the point that parts per trillion in a liquid sample and even one atom of a contaminant in a gas sample may possibly be detected. These levels are in marked contrast with the limit of detection at the parts per million level possible when the Food and Drug Administration (FDA) policy was initiated (Jackson 1980). Then, a contaminant present at concentrations below detectable levels was commonly assumed to cause no harm. Now, in addition to more sensitive chemistry, there is an increasing concern about the effects of low level exposures among the general population. Also, an increasingly huge volume of chemical and radioactive wastes is being generated. Thus, we live in a

---

[1]This report cites many EPA communications. For convenience and to save space those commmunications published in the *Federal Register* are cited in this format where 34007 is the page number of *Federal Register* Volume 51.

sea of low-dose pollutants, and there are inadequate resources to attempt cleanup and containment of all sources of pollutants even to the parts per million level originally used by FDA. Furthermore, to attempt such an action would be unbearably expensive and unnecessary for most pollutants.

It is important to identify and manage the significant problems early and to commence containment or remedial action measures at points of greatest potential for harm. Such considerations cannot be made accurately unless the individual pollutants are considered on a common scale. By this process, the effect of the total exposure is estimated, and decisions become more realistic.

Our primary objective, therefore, is to develop mathematical models and collect biological test data needed to develop a rationale and a methodology for establishing criteria for cleanup or waste management of both hazardous chemicals and radioactive materials. Concentrations of individual pollutants will be compared on a risk-equivalent basis. This goal reflects many subtasks. Development of a realistic and functional common scale depends upon completion of all such tasks. The "common scale" or "risk equivalent" basis is discussed in more detail in Sects. 9-11. Among several secondary objectives, the most important at this reporting is to develop criteria for 13 radionuclides and 14 chemical contaminants that have already been identified as having a high potential to be problem pollutants at ORNL sites.

Other important secondary objectives include (1) an estimation of the safety margin reflected in current EPA regulations for site contaminants, (2) the derivation of estimates of EPA regulations potentially forthcoming in the next few years and in the longer term for postclosure planning, and (3) comparisons of coefficients of risk for those site contaminants with coefficients of risk for ubiquitous environmental exposures.

Direct comparisons of toxicological potential between different chemical or physical agents can be made with a high degree of relative accuracy, even though extrapolations to assess the impact on human health are highly uncertain (Ames et al. 1987). Also, in order to help contrast widely accepted hazards from other hazards that frequently (and reasonably) become unacceptable to a significant fraction of the population, it is important to explore the possibility of expressing the toxicity of one agent relative to a toxicity standard defined with a reference agent. In this report, efforts will be made to compare contaminant levels of fugitive emissions in drinking water with contaminant levels resulting from water chlorination and with the cooking or growing processes for a few commonly consumed foods (Ames et al. 1987). If pollutant toxicity is far below the contamination levels associated with water "purification" and cooking, then it would seem that risk levels should be reasonably acceptable to most individuals.

## 3. BACKGROUND: EPA RISK ANALYSIS AND RISK MANAGEMENT

### 3.1 ABSOLUTE DECISION MAKING FOR MANAGEMENT OF HAZARD/RISK

Historically, human health hazards derived from occupational and/or environmental exposures have been analyzed and managed individually. Basically, the decision-making process has involved: identification of the potential hazard; collection of animal toxicological or human health data; analysis of the dose-response effect; collection of data on current exposures; projection of future human exposures; and addition of margins of safety judged to be adequate to span uncertainties in: (1) the dose-response analysis, (2) projected exposure scenarios, and (3) the possibility that projected exposures will involve a more sensitive human population than the human or animal population from which the hazard evaluation has been derived. Obviously, specific evaluations for individual chemicals (or hazardous agents) based on an absolute approach will not be accurate in a relative sense (40FR59567) even though the evaluations are made according to a common philosophy. A simplified schematic of the historical process for hazard evaluation and risk management is given in Fig. 1.

The Safe Drinking Water Act (SDWA), first enacted in 1974 (42USC300f, et seq.), required EPA to establish national interim primary drinking water regulations for public drinking water systems to regulate "specified contaminants which in the judgement of the Administrator, may have any adverse effect on the health of persons" [Section 1401(1)]. The SDWA required EPA to establish national primary drinking water regulations that include legally enforceable maximum contaminant levels (MCLs) or treatment techniques. In addition, the standards were to be revised based on a comprehensive assessment of potential adverse effects to derive recommended maximum contaminant levels (RMCLs). RMCLs were to be set "at a level at which, in the Administrator's judgement . . . no known or anticipated adverse effects of the health of persons occur and which allows an adequate margin of safety" [Section 1412(1)(B)]. RMCLs are not legally enforceable but represent health-based goals for regulation. EPA was charged to promulgate MCLs (or treatment techniques) for each contaminant for which an RMCL was promulgated. An MCL was to be as close to the RMCL as feasible [Section 1412(b)(3)]. As a consequence, EPA promulgated National Interim Primary Drinking Water Regulations in 1975, 1976, and 1979. Those standards covered 26 pollutants. EPA had wide discretion to select substances for regulation and to regulate each substance in an absolute sense.

EPA's drinking water criteria activities have relied on techniques of absolute decision making. These evaluations approach chemical carcinogens according to analytical models developed by the EPA Carcinogen Assessment Group (CAG) (Anderson 1983), noncarcinogens according to traditional toxicological methods (Dourson and Stara 1983; Dourson et al. 1985), and radionuclides according to methods recommended by the International Commission on Radiological Protection (ICRP) in Publication 30.

The CAG evaluation can be quite realistic (and potentially accurate) when based on reliable exposure and epidemiological data. An example of a definitive (and probably realistic) evaluation by CAG methods is found in the EPA Health Assessment Document on Chromium (EPA-600/8-83-014F), which is summarized in Appendix A. The Health Assessment Document (EPA 600/8-83-014F) recognizes the value of the chromium experience in stating that the

analysis provides a basis for estimating public health impact including a potency evaluation in relation to other carcinogens. This evaluation is in marked contrast to analyses for other chemicals based on upper limit analysis of risks to test animals.

The CAG philosophy is to err in favor of safety when human risk coefficients are derived from more incomplete data or animal bioassays (51FR34046). In this situation, the CAG approach is characteristic of a "data sparse" and "model intensive" methodology ensured by inflated margins of safety, but it does not attempt to emulate the worst case assessment (51FR34053). The CAG philosophy was devised for *absolute* decision making and readily acknowledges a lack of relative accuracy. For example, tables of risk coefficients from CAG evaluations note that "not all of the carcinogenic potencies presented in this table represent the same degree of certainty" (see EPA/600/8-83/012FF).

An example of a CAG evaluation based on very sparse animal data is the Drinking Water Criteria Document for Polychlorinated Biphenyls (report no. PB86-118312). Permissible concentrations of polychlorinated biphenyls (PCBs) in drinking water are based on an upper 95% confidence limit analysis of the maximum likelihood evaluation (i.e., $Q^*$) of the dose-response of only one rat experiment that comprised only one treated group. Obviously, the CAG analysis for PCBs is fraught with potential uncertainties. The PCB standard is one that may need numerical adjustment for a consistent margin of safety but certainly needs documented (and strong) support through a comprehensive relative potency analysis. Thus, the PCB risk coefficient can be analyzed by "data intensive" techniques in contrast to the existing EPA drinking water standard, which is based on a "data sparse" but "model intensive" evaluation.

For chemical carcinogens, the EPA water criteria activity has recommended "acceptable" concentrations for EPA-recognized carcinogens in drinking water. These recommendations are referred to as "risk specific dose" (RSD) values and are based on a concentration related to a calculated risk of $10^{-5}$ per person-lifetime (52FR21648, 52FR16982). If an acceptable risk is taken as $10^{-5}$ per person-lifetime, then from the CAG models Risk = $Q^*$ x Dose so that Dose = $10^{-5}/Q^*$ where units of $Q^*$ are in $(mg/kg/d)^{-1}$. This convention is commonly used to set criteria for contaminants in air [i.e., reference air concentrations (RACs)], water (i.e., RSDs), or food.

For noncarcinogenic chemicals, several EPA initiatives have elected to use the concept of "Reference Dose" (RfD), which is based on the assumption of a pharmacologically ineffective dose (i.e., a threshold) for each chemical (51FR21649, 52FR16982). That is, each individual test animal (or human) has some threshold below which no effect will occur. Above that threshold the individual will respond, and all individuals would be predicted to respond when dosed above the threshold of the most resistant individual. Reference doses emphasize the use of route-specific, high quality, peer-reviewed data of appropriate exposure duration. Such data are rarely available--as EPA has found. EPA has specified that reference doses cannot be based on *in vitro* studies or acute studies in animals. The RfD concept is based on a no observed adverse effect level (NOAEL) or a low observed adverse effects level (LOAEL), reduced by uncertainty/safety and modifying factors as described in Appendix B (Dourson and Stara 1983; Dourson et al. 1985; Stokinger and Woodward 1958; Jackson 1980; Gaylor 1983). The strength of chemical-specific RfDs derives from an EPA peer review and validation process.

For radionuclides in drinking water, the EPA has relied on the ICRP methods (ICRP report 30) to calculate "estimates of health risk from exposure to radioactive pollutants" (Sullivan et al. 1981). The EPA methods and ICRP report 30 are described briefly in Appendices C and D.

To summarize the background for absolute decision making: although sanctioned by EPA and EPA's organized expert committees, no common scale of hazard or risk can be extracted from EPA's "absolute" evaluations of chemical carcinogens, chemical noncarcinogens, and radionuclides, and EPA's *Superfund Public Health Evaluation Manual* cautions against "comparable scales."

Each of EPA's rulemakings, as based on absolute decision making, is likely to be consistent with "protection of human health" for that particular hazardous substance. But, because pollution-stimulated disease rates depend upon the total temporal exposure to *all* toxic insults acting simultaneously and sequentially, "protection of human health" cannot be effected by careful consideration of only a few substances while ignoring hundreds, or thousands, of other substances, which are deferred primarily because of "data gaps" or lack of appropriate data required to associate disease rates with exposure.

The inertia of "absolute" decision making is demonstrated by the fact that EPA has set standards for only seven air pollutants (since circa 1980) because the current law mandates a pollutant-by-pollutant review based on extensive proof of health effects. The strict requirement of such data means that health protection will occur only as a remedial action or in response to "unsafe" exposures.

The Department of Health and Human Services (DHHS) (1985) has stated that "the lack of adequate data for modeling should never be an excuse for not taking or for postponing appropriate action to protect public health." This recommendation is quite inconsistent with several regulatory decisions (e.g., 52FR25721). Additionally, the American Conference of Governmental Industrial Hygienists' Threshold Limit Values (ACGIH-TLV) Committee "holds to the opinion that limits based on physical irritation should be considered no less binding than those based on physical impairment. There is increasing evidence that physical irritation may initiate, promote or accelerate physical impairment through interaction with other chemical or biologic agents" (ACGIH 1986-1987).

## 3.2 RELATIVE DECISION MAKING FOR MANAGEMENT OF HAZARD/RISK

EPA's approach to regulation has, over the past decade, begun to evolve from the "absolute" to the "relative" only in response to a number of statutory requirements.

As one example, the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) of 1980, Sections 103(a) and 103(b), requires "persons in charge of vessels of facilities from which hazardous substances have been released in quantities that are equal to or greater than the reportable quantity to notify the National Response Center. . . . Section 102(a) authoritzes [EPA] to adjust reportable quantities (from statutory or previously adjusted values) for hazardous substances and to designate as hazardous substances [those which] may present substantial danger to the public health or welfare or the environment" (50FR13456; 51FR34534; 52FR8140).

The release of a reportable quantity (RQ) thus serves merely as a trigger to determine whether a spill of a hazardous substance should be

reported. To meet the tasks of adjusting RQ values from the statutory levels of one pound, the EPA began a large analysis of "relative" comparisons for hundreds of hazardous substances. Relative comparisons are typically presented in two cosmetically distinct, but functionally equivalent, forms: in one form the numerical rating of some characteristic of an agent is compared directly with the numerical rating of the same characteristic of a standard or reference agent, viz., relative potency for chemicals, relative biological effectiveness for ionizing radiations, and horsepower for the capacity to work. A second relative comparison is to arbitrarily define categorical bounds and sort agents accordingly. This is the approach used by the EPA to adjust RQ values.

To adjust an RQ value from the statutory level of one pound for a hazardous substance, six characteristics are considered: aquatic toxicity, ignitability, reactivity, acute toxicity, chronic toxicity, and potential to "cause" cancer. An RQ is set for each characteristic and may be modified to consider biodegradation, hydrolysis, and photolysis. The RQ for a substance is based on the most potent ranking in the six classes of consideration. An RQ is then categorically assigned as 1, 10, 100, 1000, or 5000 pounds.

For acute toxicity, the RQ is based on the lowest categorical rating from oral, dermal, and inhalation routes of exposure.

For chronic toxicity, the RQ is based on the categorical comparisons of the product of the minimum effective dose ranked on a scale of 1 to 10 and the severity of the reaction expressed on a scale of 1 to 10.

For cancer, the RQ is based on the weight-of-evidence and the potency as computed by the CAG models (e.g., EPA-600/8-83-014F). EPA's weight-of-evidence classification system comprises five groups (51FR21667). Group A indicates proven human carcinogens. Group B indicates probable human carcinogens. Group C comprises possible human carcinogens including agents with limited evidence of animal carcinogenicity. Group D includes agents that cannot be classified because no data or insufficient data are available. Group E includes chemicals for which there are adequate negative animal bioassays. Because carcinogens differ in weight of evidence, the EPA believes that establishment of a single across-the-board risk level is not appropriate and has proposed to set a reference risk level "For known and probable human carcinogenic agents (Classes A and B) . . . at the $10^{-5}$ risk level . . . for Class C carcinogens . . . $10^{-4}$." For Class C carcinogens the RQ is based on NOAEL/1000 (51FR21666).

EPA's decision to set RQ values according to a risk of $10^{-4}$ for Class C carcinogens, $10^{-5}$ for Classes A and B carcinogens (51FR21666), and $10^{-6}$ for the RCRA land disposal restriction regulations (51FR1603) is very subjective and quite inconsistent with recommendations by the DHHS (1985).

The strengths of the RQ-based toxicity factors derive from EPA's peer review of experimental data and the attempt to select data to set the lowest value (from six characteristics) for an RQ. The RQs for toxicity considerations (acute, chronic, cancer) are based on peer review and are not intended to reflect worst-case situations. Obviously, the RQ approach is weakened seriously by gaps in needed data, subjectivity in mechanisms of evaluation, and instability of the "data sparse" and "model sparse" approach.

Perhaps in response to congressional complaints and public comments or to operationally distinguish between "carcinogens" and "potential carcinogens," EPA has proposed to modify the methodology for adjusting the RQ even though the EPA's *Proposed Guidelines for Carcinogen Risk Assessment*

states explicitly that "It should be emphasized that calculation of quantitative estimates of potential cancer risk does not require that an agent be a human carcinogen" (49FR227). The proposed rule says,

> The CERCLA methodology is not a risk assessment and it does not yield an absolute measure of harm. Rather, the methodology simply represents a means of sorting potentially carcinogenic substances into categories which may then be equated to RQ levels. . . .

During the quantitative stage, the Agency uses the available data to estimate the dose of a hazardous substance associated with a lifetime increased cancer risk of 10% ($ED_{10}$).

The risk end point (e.g., incidence, mortality, etc.) is poorly defined because the data used to make the evaluation may vary from chemical to chemical. For example, if animal data are used it is not uncommon to combine hyperplastic nodules with liver carcinomas so that the end point would in essence be incidence of pathologically abnormal livers. The estimated dose is then used to calculate a potency factor (F) where F equals $1/ED_{10}$ (52FR8144).

One of three categories is assigned based on the magnitude of F. Next, the categorical assignment may be increased or decreased one level depending upon weight of evidence. This determines the RQ of 1, 10, or 100 pounds (52FR8144) for carcinogens in contrast to the five-tiered evaluation for noncancer considerations.

As a second example of relative decision making, CERCLA (42USC9601ff) requires the development of "methods for discovering and investigating facilities at which hazardous substances have been disposed of or otherwise come to be located." CERCLA [Section 105(8)(A)] mandates that EPA formulate:

> Criteria for determining priorities among releases or threatened releases throughout the United States for the purpose of taking remedial action and, to the extent practicable taking into account the potential urgency of such action, for the purpose of taking removal action. Criteria and priorities under this paragraph shall be based upon relative risk or danger to public health or welfare or the environment, in the judgment of the President, taking into account to the extent possible the population at risk, the hazard potential of the hazardous substances at such facilities, the potential for contamination of drinking water supplies, the potential for direct human contact [and] the potential for destruction of sensitive ecosystems. . . .

To meet the requirements of CERCLA, EPA originally used a hazard ranking system (HRS) (47FR21330) developed by the Mitre Corporation as a means of prioritizing potentially hazardous sites. The HRS method is a means of "relative" decision making. The toxicity models used in the HRS are based on the Sax index of toxicity. The Sax index for any particular chemical is a categorical assignment of 0, 1, 2, or 3, based on acute toxicity as judged by the severity of the toxic response and the duration of the response. The Sax index does not reflect the dose required to induce toxicity.

The HRS model has also been criticized because (1) chronic toxicity and carcinogenicity to humans were not reflected by the Sax index, (2) mutagenic and teratogenic effects were not considered, (3) insufficient stratification of hazards resulted because only four categories of toxicity were considered, and (4) a particular site was scored based on the *one* most toxic chemical known at that site--even though CERCLA lists 717 hazardous substances. The Superfund Amendments and Reauthorization Act (SARA) requires that HRS be revised so that "to the maximum extent feasible, [it] accurately assesses the relative degree of risk to human health and the environment posed by sites and facilities subject to review" [Section 195(c)(1)]. SARA requires that revisions to the HRS be promulgated not later than April 17, 1988, and enacted and implemented by October 17, 1988.

Section 110 of SARA amends Section 104 of CERCLA and requires EPA, along with the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a list of at least 100 hazardous substances, in order of priority, that are most commonly found at sites on the National Priorities List (NPL) and that pose the most significant potential threat to human health. The first list has been published (52FR12866).

A third example of relative decision making is reflected by the requirements of the SDWA as amended in 1986. In that rule RCMLs were renamed maximum contaminant level goals (MCLGs), but the definition did not change. The amendments require EPA to regulate 83 contaminants in drinking water by 1989 (52FR25720). EPA has been given the option to substitute up to seven contaminants. Also, the amendments require the EPA to establish a drinking water priority list (DWPL) of contaminants that may have any adverse effects on the health of persons and that are known or anticipated to occur in public water systems and may therefore require regulation. In order to make substitutions, the EPA administrator must determine [after notice and opportunity for comment (e.g., 52FR25720)] that "regulation of the substitutes . . . is more likely to be protective of public health (taking into account the schedule for regulation)" than regulation of the originally listed contaminants that would be removed from the list of 83 [Section 1412(b)(2)]. In selection of the DWPL, EPA must consider, at a minimum, substances referred to in Section 101(14) of CERCLA and pesticides registered under the Federal Insecticide, Fungicide, and Rodenticide Act [Sections 1412(b)(2)(C)-(D) and 1412(b)(3)(A)-(B)].

Thus, under the SDWA the EPA is mandated to consider potential pollutants that could easily number into the thousands. Even facing analysis and regulatory problems of such a magnitude, the EPA is reluctant to change from its historical background of "absolute" decision making:

> In response to tasks required by the SDWA and the DWPL, the EPA believed it was not appropriate to use a specific formula to apply selection criteria because of the many variables associated with contaminants in drinking water; however, the Agency developed a decision-making "logic train" which incorporates selection criteria into a framework on which to make determinations. . . . Given the variability associated with human health and exposure aspects of drinking water contaminants and the directives of the SDWA, EPA believes that decision criteria must remain flexible, so that a case-by-case decision can be made for each contaminant. . . . Essential factors in the analysis are:

- Are there sufficient health effects data upon which to base an MCLG?
- Are there potential adverse health effects from exposure to the contaminant via ingestion?
- Does the contaminant occur in drinking water? Has the contaminant been detected in significant frequencies and in a widespread manner?
- If data are limited on the frequency and nature of contamination, is there a significant potential for drinking water contamination? (52FR25720).

The EPA attempts to evaluate each of these four factors in an absolute sense. For example, there are large gaps in most health effects data. Only a few chemicals are categorized adequately so that an MCLG can be based directly on health effects data, because "the health basis . . . is normally either adequate human data or data from an adequate subchronic or chronic toxicity study in an appropriate test animal. . . . If no such data were available and none were expected to be available within the next one to two years, the contaminant was also considered as a candidate for replacement" (52FR25720).

Based primarily on data gaps, the EPA has proposed to substitute other chemicals in place of aluminum, sodium, dibromomethane, molybdenum, and vanadium.

Even for those chemicals with human or animal data, EPA's analysis usually depends upon complex mathematical models and mechanistic assumptions used as an underpinning for the mathematics. Thus, for almost any chemical of concern (e.g., drawn randomly from the CERCLA, SDWA, DWPL, or Chemical Abstracts list), the expectation is that "insufficient" data will be available in order to implement reasonably accurate "absolute" decision-making techniques. In addition, Ames, Magaw and Gold (1987) have considered "implications for decision making" as a product of "ranking possible carcinogenic hazards." They concluded that it is not scientifically credible to use the results from rodent tests done at the maximum tolerated dose to directly estimate human risks at low doses.

With regard to the second factor, as to whether there are potential adverse health effects as a result of ingestion, the answer must be an unequivocal "yes"--for any chemical, including distilled water. Toxicity results from "excessive" exposure to any chemical agent. Thus, in essence, EPA will be operationally bound to execute SDWA and DWPL mostly through considerations of an agent's potential for contamination of drinking water.

To summarize the background for relative decision making: By legal mandate, EPA must use relative methods of decision making for management of human health risks. To meet some of these needs, the EPA is considering using the toxicity factor data base used to promulgate reportable quantities. Each of those applications is likely to be dependent upon the strengths and weaknesses of the basic RQ methodology described earlier.

Even with a congressional mandate to consider hazardous substances in a "relative" manner, the EPA has elected to do so with the methods and data used for "absolute" decision making. Here also it is accurate to note that no common scale of hazard or risk can be extracted from EPA's "relative" evaluations of chemical carcinogens, chemical noncarcinogens, and radionuclides.

## 4. HAZARD MANAGEMENT VS RISK AVERSION

Health-effects-based decision making can operationally be separated into hazard and risk considerations. In brief, hazard evaluation or assessment may involve a rapid evaluation based on experience and/or readily available data. The response to the threat of a hazard (or management of the hazard) is usually relative in nature (i.e., setting priorities without currently defined regulatory or compliance responsibilities), and the magnitude of the management activity usually exceeds the magnitude of the evaluation by extremely large factors. In contrast, risk analysis has traditionally involved an analysis of potential harm based on an exhaustive evaluation of all relevant data and an intensive mathematical analysis of those data designed to combine biological and physical laws into a calculational analogue model. The calculational model can then be evaluated for different input variables such as exposure time or intensity of the insulting agent in order to predict a probable outcome for either untested exposure conditions or untested human populations hypothesized to be at risk. Frequently, risk evaluation is complex and may equal the effort of risk management--thus, the logic for the unbalanced title to this section. The purpose of risk evaluation is frequently regulation or "proof" of compliance with official regulations or standards. The hazard and risk aspects of health-effects-based decision making are illustrated in Fig. 2.

As illustrated in Fig. 2, some may prefer to describe hazard by relative comparisons and risk by absolute comparisons. Characteristics of each schema are listed. It is readily obvious that some characteristics of each logic pathway are more desirable than others. The desirable characteristics for rapid screening (or prioritizing chemical exposures) are indicated by X's on Fig. 2.

Listed at the bottom of Fig. 2 are additional characteristics useful for setting priorities. Thus, one view of an idealized hazard evaluation model would be to maximize incorporation of the desired characteristics and to minimize incorporation of the undesired characteristics--as indicated in Fig. 2.

We have attempted to design a rapid hazard evaluation model based on vast quantities of relative potency considerations of *in vitro* and *in vivo* biological test data. As indicated in Fig. 2, this has been called the Rapid Screening of Hazard (RASH) method (Jones et al. 1985; Jones et al. 1987).

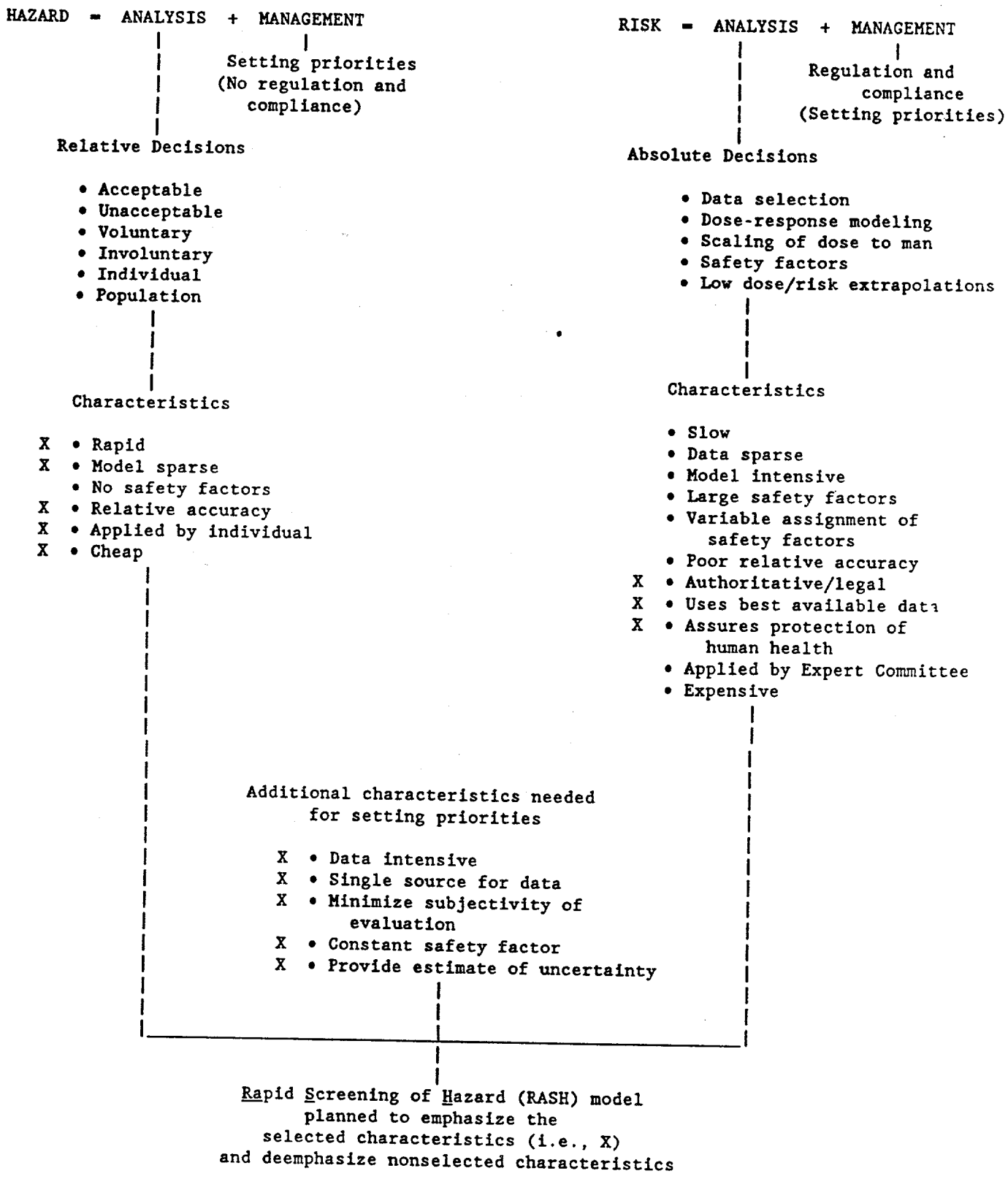



Fig. 2. Health-effects-based decision making

## 5. RAPID SCREENING OF HAZARD: INTRODUCTION OF RASH

Characteristics of a "carcinogen" cannot yet be specified in terms of chemical structure, molecular interactions, or intrinsic traits of a pathological test model. It is not clear that a mechanistic description of carcinogenesis is possible because carcinogenesis is a result of a toxic agent interacting with a biological system under a specific test protocol. The variation of the chemical or physical nature of the test agent, the biological code, or parameters of the test protocol can affect the outcome of the interaction between insult and target. In 1958, Stokinger and Woodward noted "what is or is not a carcinogen for man cannot be presently inferred from animal studies. . . . Research should be stimulated in this area of cancer research to develop minimal tolerable doses of carcinogenic agents for man." Three decades later, the observation is equally true.

Although detailed understanding of the etiological factors of cancer remains obscure, logical associations between macroscopic tissue responses and growth of cancer are strongly supported by large numbers of initiation-promotion studies. Many of these studies have been reviewed (Jones et al. 1983; Jones 1984; Ames et al. 1987). Those publications can be used to support the idea that the frequency of cancer diagnosis appears to be in direct proportion to the amount of compensatory cell proliferation required to restore tissue homeostasis following toxic and/or hyperplastic wounding of biological tissue. Put even more simply, cancer growth from subclinical lesions is proportional to wound healing. The hypothesis requires that all insults that stimulate compensatory cell proliferation (in mixed-field exposures to environmental chemicals) should be evaluated quantitatively as a potentiator of carcinogenesis (i.e., a cancer promoter).

The logic of the RASH methodology is summarized as follows: The etiological molecular processes of late somatic effects such as cancers or cardiovascular diseases are much studied but incompletely understood. Correspondence between molecular interactions and human diseases has not been established; however, there is generally good correlation between DNA damage and initiation of primordial carcinogenic lesions. Furthermore, there is strong and rapidly increasing evidence that compensatory cellular proliferation in response to toxic injury is a direct quantitative measure of induced carcinogenic promotion. Significant doses of most chemicals can cause irritation, focal necrosis, compensatory cellular proliferation, and a general progression of toxic response symptoms ranging from acute transitory effects to late (or chronic) somatic effects. Because of these factors and because of the general correspondences outlined above, the relative potency of a chemical should maintain some degree of consistency when measured in various biological models, spanning molecular interactions to organ pathological measures, when pharmacological toxification/detoxification processes have been taken into account. Of course, some variability must occur depending on the pathological effect observed, dose level, dose rate, species, strain, age, nutrition, environmental conditions, pharmacological rate constants, enzyme inventory, membrane permeability, route of chemical intake, chemical carrier or aerosol used, pathological protocol of diagnosis, and other factors. These and many other processes can induce variability in the potency of one particular chemical relative to a reference chemical. In many cases the range may be small, but in some cases the range may encompass orders of magnitude. Usually in any particular biological study, the level of response is highly sensitive to only one or a few of the listed variables.

Thus, one observes a fairly stable relative potency value instead of a potency value that has great variability. However, experimental and physical parameters can be adjusted to illustrate the extreme effect. We consider the range of uncertainty to be one of the *extremely useful parameters of human risk* associated with a given chemical. The range in response derived from variability in relative potency should be useful in addressing the range of response in man as estimated from extrapolations of test data and also the range of individual sensitivity of animals within a given biological test model. The other scoring methods we have reviewed have no comparable measure of uncertainty.

With regard to uncertainties due to model extrapolations, the Executive Committee of the DHHS has recommended that model-based estimates "should not be considered by themselves without the major uncertainties associated with the generation of such estimates being characterized. This characterization should be an integral part of the estimation process and not just a caveat to the process, which is given little or no consideration. Otherwise, quantitative estimates are likely to be accorded a degree of scientific precision that may be unwarranted" (DHHS 1985).

The relative potency approach provides a framework for the use of multiple models and data bases to estimate the potential impacts of chemicals about which we know little. For example, if sufficient human exposure-response data exist, it is possible to make direct estimates of health risk in the exposed population. If sufficient human data are not available, the relative potency method can be used to consider all relevant biological test data as long as the chemical of concern and the reference chemical have both been tested in the same biological model (preferably under the same experimental conditions). In this framework, we can also choose different models of dose response and judge the predictability of various subhuman systems as indicators for human health effects. Extensive review of the support for this unifying approach to risk analysis has been published by Jones et al. (1983, 1985, 1987) and Ames et al. (1987). This section presents a brief summary of the RASH method. The discussion may seem excessive, but because the RASH method is unique and in marked contrast to EPA regulatory methods, the given level of detail may be appreciated by some readers.

The RASH method attempts to maximize the relative accuracy of comparisons between the results of various *in vitro* and *in vivo* biological test models when treated with different chemicals. Thus, the influence or effect of safety factors, uncertainty factors, upper confidence bounds, modifying factors, etc., is minimized in the RASH analysis. However, each chemical, whether classified as a carcinogen or not, is evaluated as potentially amplifying the effect of exposure to natural or technologically concentrated carcinogens for human exposures to complex mixtures of environmental pollutants. Acute toxicity data as measured in various test models do not provide information that is directly suited to assessment of human health risks. However, the test results can be used to evaluate the relative toxicity of a compound and to aid in the determination of treatment doses to be used in tumor studies. Thus, doses applied in tumor studies are not independent of acute toxicity, and, as a consequence, relative potency-based comparisons for tumor studies may resemble relative potency estimates based on toxicity for a variety of reasons (Jackson 1980). These reasons are mentioned frequently in various sections of this report.

One basic difference between RASH and the EPA-CAG methods is described as follows: A hypothetical dose response for a reference carcinogen is illustrated in Fig. 3. In Fig. 3, circles simulate biological test data, the function resembles the multistage model used by EPA (Anderson 1983), and the dashed curve is the upper 95% confidence limit of the low-dose slope (i.e., $Q^*$). $Q^*$ derives from EPA-CAG models (Anderson 1983). The magnitude of the separation between $Q^*D$ and R(D) varies from carcinogen to carcinogen. Hence, for chemical ranking and/or site prioritization, it is expected that comparisons of R(D) values will be of greater relative accuracy than comparisons of $Q^*D$ values. Also, prioritizing chemical sites or ranking complex mixtures according to

$$R = Q_1 \sum_{i=1}^{n} D_i \times RP_i$$ should be strongly preferred over $$\sum_{i=1}^{n} Q_i^* D_i$$, where

$Q^* = 0$ for all noncarcinogens. In fact, $R = Q_1 \sum_{i=1}^{n} D_i \times RP_i$ conforms with

the harmonic mean analysis proposed by EPA for mixtures of hazardous wastes (51FR5472; Jones et al. 1987) and used extensively by the ACGIH to calculate TLVs for simultaneous exposure to multiple agents.

The strategy of the RASH method in deriving estimates of permissible concentrations is to compute relative potency values for each chemical of interest. This calculation provides a high degree of relative accuracy so that the chemicals can be judged on a common scale (Jackson 1980). However, the scale is unitless and does not address absolute decision making (i.e., permissible concentrations in environmental media). The bridge to this step is achieved by choosing as the reference or standard chemical a chemical that has an abundance of test data in various *in vitro* and *in vivo* test models and that has a human-based risk coefficient or dose-response function. Next, each of the various chemicals is computed into an equivalent dose, with respect to toxicity, of the reference chemical. In this fashion, each chemical being evaluated has relative accuracy, yet its risk coefficient (which we derive) or its permissible concentration theoretically has roughly the same margin of safety as that derived by the standard setting body for the reference chemical. Obviously, random errors and unpredictable errors in experimental design can vary the magnitude of safety for any interviewing chemical. "Interviewing chemical" is used in a descriptive sense to denote a chemical being assayed for toxicological potency. That chemical may or may not be produced or used for industrial processes, depending upon its toxicity. The logic of RASH-based analysis of toxicological data is shown in Fig. 4.

The RASH analysis of Registry of Toxic Effects of Chemical Substances (RTECS) data is rapid and inexpensive. However, the philosophy of the relative potency-based RASH analysis can be hypothesized to lead to inconsistent results with those estimates deriving from expert committees such as CAG, Water Criteria of EPA, and the ACGIH. Therefore, it is desirable to compare RASH-based calculations with those of expert committees.

Obviously, the highest degree of stability between RASH estimates and the expert committees would be expected for chemicals that have been used

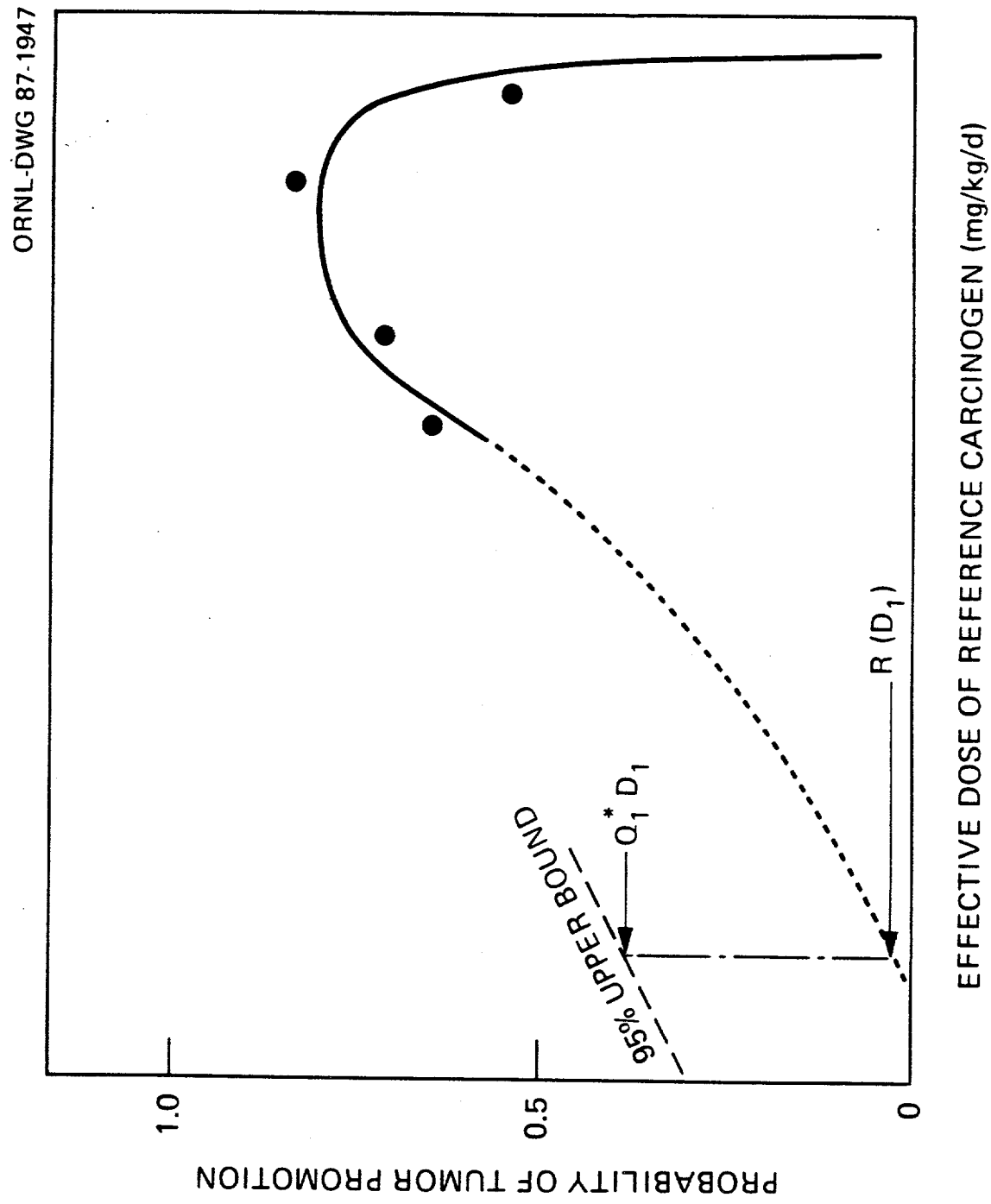



Fig. 3. Typical schematic of EPA-CAG dose response model.

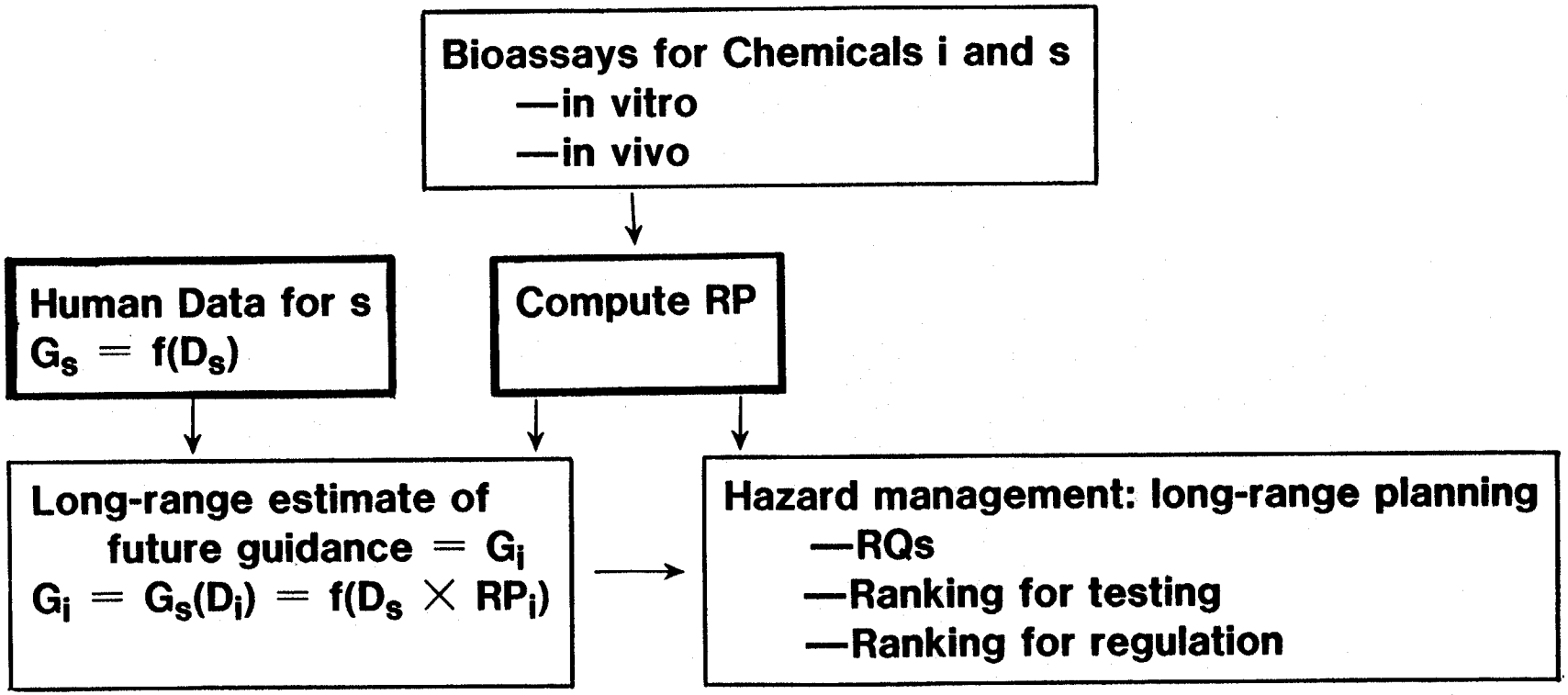



Fig. 4. Hazard evaluation: rapid screening hazard (RASH) approach.

widely and tested in numerous bioassays. A simple comparison for benzene, tetrachloroethylene, trichloroethylene, toluene, and vinyl chloride supports this assumption as shown in Table 1. Values in Table 1 illustrate "mature" regulations that are unlikely to be changed significantly unless a level of risk different from $10^{-5}$ per person-lifetime is taken as a decision point. Also, the highest degree of inconsistency between RASH and the expert committees would be expected for chemicals that have not been suspected as increasing the capacity to amplify cancer frequency and that have been used in many industrial applications, without impacting worker health. Those chemicals can be previewed by examples of ethyl benzene, dichlorobenzenes, pentachlorophenol, phenol, and phthalate esters. Those comparisons are shown in Table 2. These and many other chemicals are of current concern and the example that CAG reevaluated dichlorobenzene (230/0.1, or 1000-fold) lower than previous analyses indicates that regulatory decision making based on absolute methods is potentially subject to rapid and large revision.

To date about 300 different substances have been scored by RASH for various applications (Jones et al. 1987; Barnthouse et al. 1986; Jones et al. 1985; Easterly 1987; Easterly and Glass 1987; Watson et al. 1987). Thus, it was desirable to test whether RASH-based estimates of the median relative potency for the interviewing chemical were consistent with relative potency values that we derived from ratios of CAG, EPA Water Criteria, and ACGIH-TLV values. Those comparisons are summarized in Table 3 and are shown as bar charts in Fig. 5. From Table 3 and Fig. 5, it seems that RASH-based estimates are as consistent with estimates deriving from one expert committee as the estimates of one expert committee are with those from a second expert committee. Thus, it seems reasonable to use a RASH-based methodology to assess the toxicity of potential ORNL pollutants and as the basis of a "common scale" for mixed-waste considerations.

**Table 1. Examples: Permissible concentrations of well-known chemicals in drinking water (mg/L)**

| Chemical | RASH | CAG | EPA-water |
|---|---|---|---|
| Benzene | 6 | 7 | 15 |
| Tetrachloroethylene | 25 | 8 | 2 |
| Trichloroethylene | 38 | 27 | 21 |
| Toluene | 8 | | 12 |
| Vinyl chloride | 97 | 20 | 520 |

Table 2. Examples: Predictions of future permissible concentrations for drinking water ($\mu$g/L)

| Chemical | Current EPA-water | Prediction RASH | Current CAG |
|---|---|---|---|
| Ethyl benzene | 1100 | 1 | |
| Dichlorobenzenes | 230 | 3 | 0.1 |
| Pentachlorophenol | 140 | 0.3 | |
| Phenol | 3400 | 1 | |
| Phthalate esters | 5000 | 100 | |

Table 3. Relative potency values derived from EPA-CAG (1985), ACGIH-TLV's, Criteria Documents, and the RASH analysis of the RTECS data base were compared chemical by chemical, one method against another. Only individual chemicals were considered--chemical classes were excluded from these comparisons. The number of chemicals ranges from 24 to 64 because both methods compared must have evaluated the same chemical.

| Methods compared | Number of chemicals | Inconsistency rate[a] | Variability factor[b] | Mean log-ratio[c] | 10% - 90% log-range[d] | Central 80% log-spread[e] |
|---|---|---|---|---|---|---|
| ACGIH - CAG | 24 | 0.08 | 5.1 | 0.88 | -1.4 to 2.7 | 4.1 |
| RASH - ACGIH | 64 | 0.06 | 0.8 | -0.02 | -2.7 to 2.4 | 5.1 |
| RASH - CAG | 33 | 0.12 | 2.0 | -0.73 | -3.8 to 1.7 | 5.5 |
| Crit. Doc. - CAG | 27 | 0.33 | 1.5 | 1.3 | -2.9 to 4.9 | 8.0 |
| Crit. Doc. - ACGIH | 35 | 0.40 | 4.7 | -1.3 | -8.2 to 4.6 | 12.8 |
| RASH - Crit. Doc. | 39 | 0.46 | 5.4 | 0.33 | -6.7 to 5.9 | 12.6 |

[a]Method A different from Method B more than 50-fold.

[b]Computed according to $\frac{1}{N}\sqrt{\sum}$ [(Method A - Method B) **2/(Method A * Method B)].

[c]Computed according to $\frac{1}{N}\sum$ log (Method A/Method B).

[d]The central 80% range of values of log (Method A/Method B) are in this range.

[e]Log spread of the 80% range in Column 6.

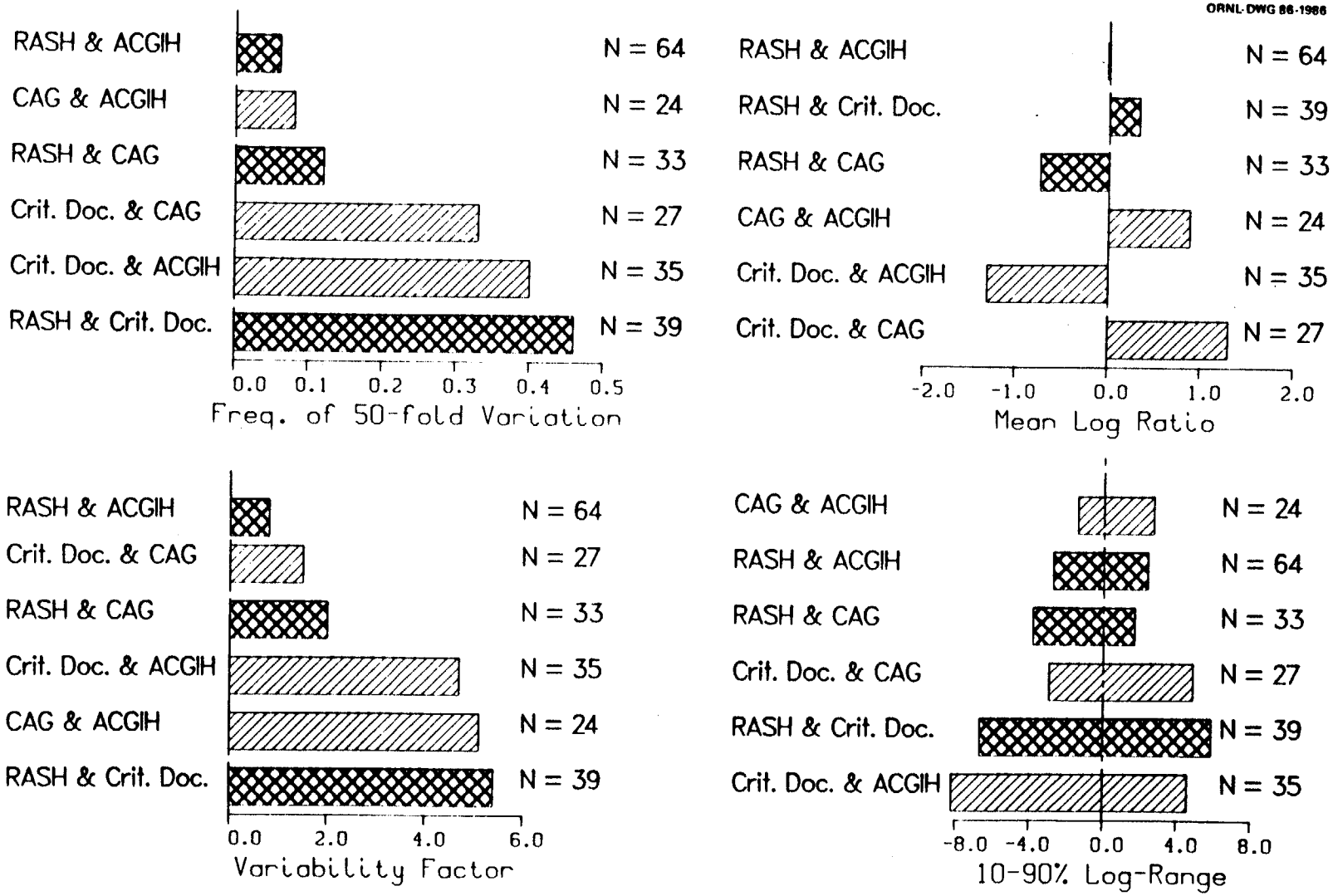



**Fig. 5. Comparisons of the consistency of how a list of chemicals is scored by one activity relative to a different activity.** Scoring activities include RASH, ACGIH-TLV, EPA-CAG, and EPA water criteria.

## 6. INITIAL POLLUTANTS SELECTED FOR WATER CRITERIA DEVELOPMENT

Thirteen radionuclides and 14 chemicals have been identified as possible ORNL pollutants. As RAP activities continue, it is expected that additional pollutants will be identified. Those 27 agents are listed in Table 4. Six of the 14 chemicals have been evaluated for potential carcinogenicity by the International Agency for Research of Cancer (IARC) (1982). The IARC's conclusions are summarized in Table 5.

The EPA-CAG (1985) has estimated risk coefficients for 54 chemicals. Those evaluations include five of the six IARC-classified chemicals (lead excluded). CAG evaluations are summarized in Table 6. Table 6 also includes CAG evaluations for acrylonitrile, arsenic, benzene, benzidine, and cadmium. These five chemicals are not expected to be problems for ORNL but are included in Table 6 because CAG risk coefficients for these chemicals are based on actual human data. Risk coefficients for the 49 other CAG chemicals are based on animal data.

Only a few chemicals have risk coefficients based on human data. These chemicals can serve as relative "benchmarks" or standards (i.e., through relative potency adjustments) in order to compare chemicals having risk coefficients based on animal bioassay data with chemicals having risk coefficients based on actual human exposures. Also, relative potency provides a bridge to use *in vitro* or acute response data to derive estimates for humans exposed to those chemicals for which we have no human or chronic animal data. This relative potency-based comparison is necessary in the development of the methodology to establish criteria for evaluating toxic chemicals, carcinogenic chemicals, and radiochemicals on a risk-equivalent basis.

Table 4. Pollutants selected for water quality criteria development

| Radionuclides | Chemicals |
|---|---|
| $^{3}H$ | Barium |
| $^{60}Co$ | Chloroform |
| $^{90}Sr$ | Chromium |
| $^{99}Tc$ | Cresols |
| $^{137}Cs$ | 2,4-Dimethylphenol |
| $^{154}Eu$ | Ethylbenzene |
| $^{232}Th$ | Lead |
| $^{233}U$ | Mercury |
| $^{235}U$ | Methylene chloride |
| $^{238}U$ | Naphthalene |
| $^{239}Pu$ | Nickel |
| $^{241}Am$ | PCBs |
| $^{244}Cm$ | Toluene |
| | Xylenes |

**Table 5. Potentially "carcinogenic" chemicals classified by the International Agency for Research on Cancer (IARC)**

| Chemical | Evidence stated by IARC[a] |
|---|---|
| Chloroform | Conclusions limited by experimental design |
| Chromium and compounds | Based on sufficient epidemiological data |
| Lead | Inadequate data to evaluate role of exposure |
| Methylene chloride | Inadequate data to evaluate role of exposure |
| Nickel | Conclusions limited by test models |
| PCBs | Conclusions limited by experimental design |

[a]"Weight of the Evidence" is presented as sufficient, limited, or inadequate.

**Table 6. The EPA-CAG-derived risk coefficients for several compounds of interest[a]**

| Compound | Evidence of carcinogenicity[b] | | Risk coefficient[c,d,e] $(mg/kg/day)^{-1}$ |
|---|---|---|---|
| | Human | Animal | |
| Acrylonitrile | L | S | 0.24(W) |
| Arsenic | S | I | 15(H) |
| Benzene | S | S | 0.029(W) |
| Benzidine | S | S | 234(W) |
| Cadmium | L | S | 6.1(W) |
| Chloroform | I | S | 0.07(O) |
| Chromium VI | S | S | 41(W) |
| Methylene chloride | I | L | 0.00063(I) |
| Nickel | L | S | 1.15(W) |
| PCBs | I | S | 4.34(O) |

[a]This table is an extraction of CAG estimates for chemicals having risk coefficients based on some human data and CAG estimates for the ORNL site contaminants which are based on animal data.

[b]L = limited evidence; S = sufficient evidence; I = inadequate evidence.

[c]Animal slopes are 95% upper-bound estimates. Human slopes are point estimates based on the linear no-threshold model. (W) = human occupational data; (H) = human drinking water data; (I) = animal inhalation data; (O) = animal oral data.

[d]Not all of the carcinogenic potencies represent the same degree of certainty. Details of CAG factors can be found in EPA/600/8-82/005F or other EPA 600-series documents.

[e]The risk is calculated by $R = S \times D$, where R is the increased probability of risk per unit lifetime, S is the numerical value shown with units of $(mg/kg/day)^{-1}$, and D is dose in units of (mg/kg/day).

## 7. EXISTING CRITERIA FOR ORNL POLLUTANTS

Existing criteria derived from various EPA activities are shown in Table 7 for the ORNL chemicals. As seen in Table 7, some of the estimates for one chemical vary by two or three orders of magnitude.

This variation is fairly typical of how "mature" regulations for a chemical are more protective than initial or "infant" regulations for the same chemical. Columns of Table 7 are more or less chronological with respect to publication date, but the underlying philosophies (which demonstrate mature vs infant regulations) of the various studies are not correlated with the dates of publication. Thus, even though infant and mature criteria are reflected in values in Table 7, it is difficult for the reader to readily view that transition. In 1978, only 25 chemicals were considered to be carcinogenic to man, but less than a decade later, Sittig (1985) listed 178 chemicals as "suspected," "potential," or "proven" carcinogens. Typically, a chemical reclassified from an animal carcinogen to a human carcinogen will be regulated ten-fold more strictly. A reclassification from a noncarcinogen to a human carcinogen would likely be regulated 1000-fold more strictly. Reclassification from a noncarcinogen to an animal carcinogen could be expected to result in a 100-fold decrease. These factors are frequently low and could be ten-fold higher for specific chemicals.

Typically only a small fraction of the universe of toxic chemicals is regulated in drinking water supplies. CAG has evaluated 54 chemicals and the Environmental Criteria and Assessment Office (Cincinnati, OH) of the Office of Health and Environmental Assessment has prepared a series of 58 Health Effects Assessments (HEAs) for the Office of Emergency and Remedial Response (EPA/540/S1-86/059).

Over 700 contaminants have, however, been identified in water, and Congress is mandating that many new regulations will be forthcoming (e.g., Cong. Record, H2326 May 5, 1986; H2633 and H2637 May 13, 1986; S6285 May 21, 1986). In addition, the General Accounting Office has charged that "EPA does not know whether it is controlling 90 percent of the existing hazardous wastes--or 10 percent; likewise, it does not know if it is controlling the wastes that are most hazardous" (*Toxic Materials News*, January 21, 1987).

Other regulatory activities have been summarized in Sect. 3. Thus, it is obvious that increasingly lower permissible concentrations are to be expected for many chemicals currently regulated. In addition, the number of chemicals regulated is likely to increase exponentially. Early in the regulatory process, a chemical is likely to be evaluated based on its capacity to induce acute symptoms of toxicity. As experience is gained with a particular chemical, considerations shift to chronic toxicity and late somatic diseases such as cancer. The common use of acute and chronic toxicity should be recognized as quite distinct from acute and chronic modes of exposure. For example acute exposure can lead to cancer, i.e., chronic toxicity. The transition of regulations through the acute to chronic disease concern is analogous to "infant" regulatory criteria (when incomplete knowledge of human health effects data is available) as opposed to "mature" regulatory criteria based on a long and safe experience with a particular chemical. The distinction between infant and mature regulations is developed more extensively in Sect. 15. Also, future regulations will at some point in time need to rely on the outcome of a predictive battery of bioassays (perhaps mutagenesis models) for exposure situations too complex to analyze chemical by chemical.

Table 7. Sample of permissible water concentration values for selected chemicals deriving from various EPA activities.[a] It may be observed from this tabulation that the EPA may recommend different permissible concentrations and/or different acceptable levels of risk depending upon the activity of concern.[b]

| Chemical | Water criteria (Sittig 1980) (μg/L) | EPA drinking water criteria documents (μg/L) | EPA-CAG 1985 (μg/L) | EPA 40 CFR Part 261 (51FR21673) (μg/L) |
|---|---|---|---|---|
| Barium | | 1,790 | | 1,000 |
| Chloroform | 2.1 | | 5 | 5 |
| Chromium | 0.008 | | | 50 |
| Chromium VI | 0.008 | 170 | 0.008 | 50[c] |
| m,o,and p Cresol | | | | 2,000 |
| Ethylbenzene | 1,100 | 3,400 | | |
| Lead | 50 | | | 50 |
| Mercury | 0.2 | | | 2 |
| Organic | 0.2 | | | |
| Inorganic | 0.2 | 5.5 | | |
| Methylene chloride | 2 | | 550 | 600 |
| Naphthalene | 143 | | | |
| PCBs | 0.00026 | 0.08 | 0.08 | |
| Toluene | 12.4 | 10,100 | | 10,000 |
| Xylene | | 2,200 | | |

[a] A wide range for a particular chemical is suggestive that official guidance may be in a period of transition. Within a particular row, lower concentrations are suggestive of "mature" regulations and higher concentrations are suggestive of "infant" regulations.

[b] In this table, chemicals that have not been classified by EPA as carcinogens are described by EPA as not contributing to carcinogenic risk below the concentrations given in this table (i.e., those chemicals are described as having a pharmacological threshold below which detoxification is complete). Values given for carcinogens are based on a level of risk of $10^{-5}$ per person-lifetime except that values from 51FR21673 are $10^{-4}$ for class C carcinogens.

[c] EPA 540/1-86/060.

## 8. RELATIVE TOXICITIES OF ORNL POLLUTANTS

The RASH method is based on deriving an array of relative potency values from a broad spectrum of biological test/screening models. The number of comparisons produced depends upon the extent that the interviewing chemical of interest has been tested and upon the isomorphism between the individual tests on the interviewing chemical and individual tests on one or more reference chemicals. Rules for matching toxicity tests in order to compute a relative potency value have been published at length (Jones et al. 1985; Jones et al. 1987) and are not reproduced here.

There are two basic ways of computing relative potency values. The one most commonly used is to compare different doses required to induce the same level of effect. The other is to compare different levels of effects resulting from equal doses.

As an example of the method where different doses are required to produce the same level of effect, one may find that a dose x (mg/kg) of a chemical has produced a particular effect in a particular species and y (mg/kg) of B(*a*)P or some other reference chemical was required to induce an equal response in the same species. The potency of the first chemical relative to the reference chemical would be y/x. Thus, if the reference chemical were considered by some regulatory agency to be acceptable at a concentration in water of 1 $\mu$g/L, then the unregulated chemical could be limited to (1 g/L)/(y/x).

Another basic comparison is illustrated when a dose x (mg/kg) of a chemical produced a toxic effect (not cancer--see Jones et al. 1987 for the time factors of carcinogenesis) in $T_1$ hours, but x (mg/kg) of B(*a*)P caused the effect in $T_2$ hours--the potency of the interviewing chemical could then be taken as $T_1/T_2$ that of B(*a*)P. Some RASH comparisons will require simultaneous application of these basic techniques. Potency comparisons are computed in gram-type units because mole or ppm units are not defined for complex mixtures. It is important not to compute some relative potency values in gram units and others in molar or ppm units. The scales are different depending upon the ratios of the molecular weights. The number of successful matches can be increased by using multiple reference or standard chemicals, but it is necessary to correct for differences in individual potencies between the standards. Thus, one of the reference chemicals is taken as the primary standard [B(*a*)P in this paper] and matches with the secondary standards are corrected to the numerical scale of the primary standard.

For previous applications, B(*a*)P was taken as the standard or reference chemical. All other chemicals are ranked relative to B(*a*)P, even when a second standard was used to compare test results. Relative potency values less than unity indicate a chemical less toxic than B(*a*)P. In order to use epidemiologically derived standards later in this report, it may be necessary to express toxicity relative to some other standard chemical, e.g., chromium. The toxicity of the interviewing (i.e., test) chemical relative to chromium would then be computed according to

$$RP = \frac{D_{Cr}}{D_{test}} = \frac{D_{B(a)P}}{D_{test}} \left( \frac{D_{B(a)P}}{D_{Cr}} \right)^{-1} ,$$

where dose ratios are taken from previously tabulated values.

Potency factors for site pollutants relative to B(*a*)P are given in Table 8.

**Table 8. RASH scores for potential ORNL contaminants**

| Chemical | Relative potency from RTECS | | |
|---|---|---|---|
| | Median | Low[a] | High[b] |
| Barium chloride | 0.051 | 0.026 | 0.11 |
| Barium, (II) nitrate (1:2) | 0.0086 | 0.00010 | 0.028 |
| Chloroform | 0.0050 | 0.0036 | 0.0065 |
| Chromium | 3.6 | 2.0 | 13. |
| Chromium VI | 44. | 19. | 1900. |
| Cresol | 0.015 | 0.0041 | 0.027 |
| m-cresol | 0.0094 | 0.00020 | 0.045 |
| o-cresol | 0.038 | 0.00037 | 0.088 |
| p-cresol | 0.020 | 0.0024 | 0.081 |
| 2,4-dimethylphenol | 0.0058 | 0.0020 | 0.029 |
| Ethylbenzene | 0.0023 | 0.0016 | 0.0092 |
| Lead | 0.092 | 0.036 | 0.51 |
| Mercury, organic | | | |
| (aceto)phenyl | 0.23 | 0.00056 | 0.88 |
| chloroethyl | 0.083 | 0.030 | 0.23 |
| chloro(2-methoxyethyl) | 0.083 | 0.046 | 0.21 |
| chloromethyl | 0.16 | 0.11 | 0.19 |
| chlorophenyl | 0.076 | 0.032 | 0.14 |
| (3-cyanoguanidino)methyl | 0.068 | 0.055 | 2.5 |
| diethyl | 0.19 | | |
| diphenyl | 0.067 | 0.046 | 0.13 |
| Mercury, inorganic | | | |
| (I) chloride | 0.010 | 0.0044 | 0.025 |
| (II) chloride | 0.48 | 0.37 | 1.1 |
| (I) sulfate | 0.00041 | | |
| (II) sulfate | 0.071 | 0.0067 | 0.15 |
| Methylene chloride | 0.0022 | 0.00033 | 0.012 |
| Naphthalene | 0.0048 | 0.0019 | 0.010 |
| Nickel | 0.13 | 0.026 | 0.67 |
| PCBs | 0.0033 | 0.0014 | 0.0076 |
| PCBs (tumor data only) | 0.041 | 0.00032 | 2.3 |
| Toluene | 0.0038 | 0.0013 | 0.0072 |
| Xylene | 0.0035 | 0.0014 | 0.0049 |
| m-xylene | 0.0036 | 0.0012 | 0.011 |
| o-xylene | 0.0016 | 0.00096 | 0.024 |
| p-xylene | 0.0038 | 0.0012 | 0.014 |

[a]Lower bound of interquartile range.
[b]Upper bound of interquartile range.

## 9. RISK-BASED COMMON SCALE FOR CHEMICALS

An important feature of a realistic risk-based common scale is to incorporate all known accurate exposure-response epidemiological data for different compounds--including chemicals not on the ORNL site. Epidemiologically based risk coefficients would then be adjusted to account for the relative potency of that particular chemical if the epidemiologically derived risk coefficients were biased towards inflated safety margins because of data gaps. If the risk coefficient for human health effects due to any specific chemical were known to be quite accurate, then all other chemicals could be expressed in terms of an equivalent dose of that one standard. Realistically, it is not known whether any one of the human-based estimates is highly accurate so it is important to consider the risk-based common scale to potentially derive from a composite standard (e.g., acrylonitrile, arsenic, benzene, benzidine, cadmium, chromium, nickel, and tobacco smoke condensate). For consistency and realism, it is essential to reanalyze the background material and analytical models behind the risk coefficient as listed in Table 6. This step corresponds to the "standardize models of dose and hazard to maximum degree possible" box in Fig. 1. Those several analyses have not been completed to date and a tentative example will be given with the CAG risk coefficient for chromium. Thus, the risk-based common scale will be rederived based on a larger data base when the risk coefficients for the seven other chemicals have been reviewed and the algorithm for either the "best" or the "composite" standard has been established.

The CAG model for chromium is

$$\text{Risk} = \text{Dose (mg/kg/d)} \times 41\ (\text{mg/kg/d})^{-1}.$$

This value is based on inhalation and the dose in mg is actually the amount of chromium in inhaled air. Not all of that chromium becomes a body burden because the absorption efficiency coefficient is only 0.25 (see Appendix A). For a risk level of $10^{-5}$ the dose of chromium would be

$$\text{Dose (mg/kg/d)} = 10^{-5}/41\ (\text{mg/kg/d})$$

$$= 2.4 \times 10^{-7}\ (\text{mg/kg/d}).$$

The risk equation for a different chemical such as cresol, based on inhalation of chromium as an assumed standard, would be derived on the equivalent toxic dose logic, i.e.,

$$\text{Risk} = \text{Dose (mg/kg/d)} \times 41\ (\text{mg/kg/d})^{-1} \left(\frac{D_{B(a)P}}{D_{Cresol}}\right) \left(\frac{D_{B(a)P}}{D_{Cr}}\right)^{-1}.$$

From Table 8, $D_{B(a)P}/D_{Cresol} = 0.015$ and $D_{B(a)P}/D_{Cr} = 3.6$ so that the risk coefficient for inhalation of cresol (based only on inhalation of chromium as a standard) would be:

$$\text{Risk} = \text{Dose (mg/kg/d)} \times 0.17\ (\text{mg/kg/d})^{-1}.$$

The dose of inhaled cresol for a risk level of $10^{-5}$ would then be

$$\text{Dose (mg/kg/d)} = 10^{-5}/0.17 \text{ (mg/kg/d)}$$

$$= 5.9 \times 10^{-5} \text{ (mg/kg/d)}$$

in the daily volume of inspired air. Corrections for differential absorption of chromium and cresol will be shown later. Tentative sample evaluations are given in Table 9 for chromium, cresol, ethyl benzene, nickel, and PCBs.

It is important to correct values in Table 9 for absorption via inhalation and then to consider differential absorption by oral intake in order to derive a permissible concentration in drinking water on a consistent risk-equivalent basis. That is done as follows: the concentration of chromium in drinking water based on the inhalation risk coefficient and a risk level of $10^{-5}$ would be

$$\frac{10^{-5}}{41 \text{ (mg/kg/d)}^{-1}} \left(70 \text{ kg}\right) \left(\frac{\text{d}}{2 \text{ L}}\right) \left(\frac{0.25}{0.05}\right) \left(\frac{10^3 \ \mu\text{g}}{1 \text{ mg}}\right) = 0.042 \ \mu\text{g/L}.$$

For a different chemical such as cresol, the corresponding concentration in drinking water would then be

$$0.042 \ \mu\text{g/L} \left[\left(\frac{D_{B(a)P}}{D_{\text{Cresol}}}\right) \left(\frac{D_{B(a)P}}{D_{Cr}}\right)^{-1}\right]^{-1} \left(\frac{0.05}{1.0}\right) = 0.50 \ \mu\text{g/L} ,$$

where 0.05 is the oral absorption coefficient for chromium and 1.0 is the oral absorption coefficient for cresol. Tentative values are given in Table 10.

**Table 9. Tentative risk-based equivalent exposures for chromium, cresol, ethyl benzene, nickel, and PCBs. Estimates are based on inhalation of chromium, and differential absorption of other compounds is not included. This table is an intermediate step to Table 10, where differential absorption is used to put concentrations on a comparable risk-equivalent basis.**

| Risk of death | Exposure (mg/kg/d)[a] | | | | | |
|---|---|---|---|---|---|---|
| Person-lifetime | Cr | Cresol | Ethyl benzene | Nickel | PCB[b] | PCB[c] |
| $10^{-6}$ | 2.4E-8 | 5.9E-6 | 3.8E-5 | 2.7E-5 | 2.1E-6 | 6.7E-7 |
| $10^{-5}$ | 2.4E-7 | 5.9E-5 | 3.8E-4 | 2.7E-4 | 2.1E-5 | 6.7E-6 |
| $10^{-4}$ | 2.4E-6 | 5.9E-4 | 3.8E-3 | 2.7E-3 | 2.1E-4 | 6.7E-5 |

[a] Not corrected for differential oral absorption. See text and Table 10 for corrections.

[b] All classes of test data.

[c] Tumor data only.

Table 10. Tentative risk coefficients and risk-based drinking water concentrations for chromium, cresol, ethyl benzene, nickel, and PCBs. Risk levels are $10^{-5}$ (person-lifetime)$^{-1}$, and differential absorption factors are included. The values are "tentative" because chromium was arbitrarily selected as the reference standard. Future work will assess the accuracy of the chromium-based standard.

| Chemical | Oral absorption factor[a] | Risk coefficient[b] $(mg/kg/d)^{-1}$ | Concentration in water ($\mu g/L$) |
|---|---|---|---|
| Chromium | 0.05 | 8.4 | 0.042 |
| Cresol | 1.0 | 3.5 | 0.50 |
| Ethyl benzene | 0.90 | 0.095 | 3.7 |
| Nickel | 0.05 | 0.29 | 1.2 |
| PCBs[c] | 0.95 | 0.15 | 2.4 |
| PCBs[d] | 0.95 | 1.8 | 0.19 |

[a]From Appendix E.

[b]Exposure dose in mg in drinking water per kg body weight per day are quantities used to compute risk from these coefficients.

[c]All classes of test data.

[d]Tumor data only.

## 10. RISK-BASED COMMON SCALE FOR RADIONUCLIDES

Risk coefficients for premature deaths in a cohort population of 100,000 persons as a function of chronic intake expressed in units of picocuries per year of ingestion for potential ORNL radionuclides are given in Table 7 of ORNL/TM-7745. Those values are converted to the "risk coefficients" given in columnm 3 of Table 11 by dividing by $10^5$ in order to normalize to per capita risk, and by multiplying by 365 times 2 to convert years to liters of drinking water. These risk coefficients are based on a linearized dose-response model so that selection of a level of risk, e.g., $10^{-5}$/person-lifetime divided by the risk coefficient (column 3 of Table 11) produces a permissible concentration analogous to that used in Sect. 9 for chemicals. Columns 4-6 of Table 11 give concentrations in drinking water corresponding to risk levels of $10^{-6}$, $10^{-5}$, and $10^{-4}$ based on consumption of 2 L/d.

Table 11. Risk coefficients and risk-specific concentrations in drinking water (ORNL/TM-7745)

| Nuclide | Deaths in $10^5$ cohort[a,b] | Risk coefficient $(pCi/L)^{-1}$ | pCi/L for $10^{-6}$ chance of premature death | pCi/L for $10^{-5}$ chance of premature death | pCi/L for $10^{-4}$ chance of premature death |
|---|---|---|---|---|---|
| $^{3}H$ | 1.80E-07 | 1.31E-9 | 7.6E+2 | 7.6E+3 | 7.6E+4 |
| $^{60}Co$ | 1.24E-05 | 9.05E-8 | 1.1E+1 | 1.1E+2 | 1.1E+3 |
| $^{90}Sr$ | 2.17E-04 | 1.58E-6 | 6.3E-1 | 6.3E+0 | 6.3E+1 |
| | 1.46E-05 | 1.07E-7 | 9.3E+0 | 9.3E+1 | 9.3E+2 |
| $^{99}Tc$ | 1.92E-06 | 1.40E-8 | 7.1E+1 | 7.1E+2 | 7.1E+3 |
| $^{137}Cs$ | 9.22E-05 | 6.73E-7 | 1.5E+0 | 1.5E+1 | 1.5E+2 |
| $^{154}Eu$ | 6.96E-06 | 5.08E-8 | 2.0E+1 | 2.0E+2 | 2.0E+3 |
| $^{232}Th$ | 3.95E-04 | 2.88E-6 | 3.5E-1 | 3.5E+0 | 3.5E+1 |
| $^{233}U$ | 1.28E-05 | 9.34E-8 | 1.1E+1 | 1.1E+2 | 1.1E+3 |
| | 5.15E-04 | 3.76E-6 | 2.7E-1 | 2.7E+0 | 2.7E+1 |
| $^{235}U$ | 1.32E-05 | 9.64E-8 | 1.0E+1 | 1.0E+2 | 1.0E+3 |
| | 4.20E-04 | 3.07E-6 | 3.3E-1 | 3.3E+0 | 3.3E+1 |
| $^{238}U$ | 1.16E-05 | 8.47E-8 | 1.2E+1 | 1.2E+2 | 1.2E+3 |
| | 4.28E-04 | 3.12E-6 | 3.2E-1 | 3.2E-0 | 3.2E+2 |
| $^{239}Pu$ | 2.90E-04 | 2.12E-6 | 4.7E-1 | 4.7E+0 | 4.7E+1 |
| | 2.82E-03 | 2.06E-5 | 4.9E-2 | 4.9E-1 | 4.9E+0 |
| $^{241}Am$ | 2.84E-03 | 2.07E-5 | 4.8E-2 | 4.8E-1 | 4.8E+0 |
| $^{244}Cm$ | 1.69E-03 | 1.23E-5 | 8.1E-2 | 8.1E-1 | 8.1E+0 |

[a]Second values for some isotopes are for least-soluble compounds.

[b]Chronic ingestion of 1.0 pCi/year assumed.

## 11. RISK-BASED COMMON SCALE FOR CHEMICALS AND RADIONUCLIDES

Tentative risk-based drinking water concentrations for chemicals were calculated as described in Sect. 9. Concentrations were adjusted for differential absorption via the ingestion route. Values are labeled as tentative because work on the best reference standard is still ongoing. Concentrations are based on $10^{-5}$ increased mortality per person-lifetime and should compare directly with concentration values in column 4 of Table 11 for radionuclides. Sample pollutants are listed in Table 12 for an increased risk of $10^{-5}$ per person-lifetime. Because the choice of a reference standard is still being resolved, only a sample of chemicals are listed in Table 12. Both radiological and chemical models are linear, so comparisons for different levels of risk can be made as described in the heading of Table 12. Work to be completed in the next year will include additional tasks to match risk models, life table projections, and organ dosimetry between radionuclides and chemicals to the maximum degree possible.

Table 12. Example concentrations of chemicals and radionuclides associated with $10^{-5}$ probability of premature death per person-lifetime. Both radiological and chemical models are linear so that direct proportionality with dose is implied, i.e., for risk of $10^{-6}$ divide values in this table by 10. Cautiously note that values in this table are tentative until the analysis of the reference standard has been completed.

| Agent | Equivalent concentration |
|---|---|
| $^{241}Am$ | 0.48 pCi/L |
| $^{244}Cm$ | 0.81 pCi/L |
| $^{60}Co$ | 110 pCi/L |
| Chromium | 0.042 μg/L |
| Cresol | 0.50 μg/L |
| $^{137}Cs$ | 15 pCi/L |
| Ethyl benzene | 3.7 μg/L |
| $^{154}Eu$ | 2.0E+2 |
| $^{3}H$ | 7600 pCi/L |
| Nickel | 1.2 μg/L |
| PCBs[a] | 0.19 μg/L |
| PCBs[b] | 0.19 μg/L |
| $^{232}Th$ | 3.5 pCi/L |

[a]Based on all classes of test data.

[b]Based on tumor data only.

## 12. MIXED-WASTE RANKING BASED ON THE COMMON SCALE

The risk-based common scale described in Sect. 9 for chemicals and Sect. 10 for radiochemicals is ideally suited to the Hazard Index Methodology for assessing the composite action of multiple simultaneous pollutants (Walsh et al. 1978; Rupp et al. 1978; EPA 540/1-86/060). The hazard index concept is based on the simple ratio of exposure (or dose) symbolized by E divided by a regulatory or guidance value, symbolized by R, in the same units as E. A hazard index value less than unity is taken as acceptable. For i simultaneous agents, the individual hazard index ratios are summed, viz.

$$\sum_{i=1}^{n} E_i/R_i \ .$$

For multiple pollutants in drinking water, estimates of concentrations could be calculated from mathematical models or determined from chemical analyses. Values for the denominator in the hazard index ratio could be taken directly from Table 12. The larger the magnitude of the composite hazard index (i.e., the sum), the higher the potential hazard (EPA 540/1-86/060). If the cumulative hazard index is near unity based on denominator values from Table 12, then a composite risk of the order of $10^{-5}$ would be expected.

## 13. RELATIVE COMPARISONS FOR SETTING ACTION LEVELS

Setting an acceptable level of risk is highly subjective and frequently variable (Rodricks et al. 1987; Travis and Munro 1986; Travis et al. 1987; 51FR21555; 51FR1603). What is set as an official level of "acceptable" risk to an individual may be considered as officially unacceptable to a large population. Some individuals argue unrealistically for a risk-free environment. Risk-based action levels may be set differently for different industries or for voluntary and involuntary exposures (NCRP Report 91). Also, action levels may be balanced against cost-benefit considerations.

It is tempting to philosophically set some particular action level of risk such as $10^{-5}$. The EPA has traditionally used this process with different activities but has used different action levels depending upon case-by-case consideration. Because EPA has used "data sparse" and "model intensive" analogies of risk, there is no direct link between the risk assessment and the actual most realistic level of likely risk or the actual exposures commonly acceptable to most individuals. For example, the EPA criterion is 0.03 $\mu$g/L for polynuclear aromatic hydrocarbons (PAHs) in drinking water. According to the Banbury Report on Coffee (MacMahon and Sugimura 1983), B(*a*)P is found in most common foodstuffs. If those foods were regulated to the same acceptable body burden as is drinking water, then an individual would be permitted to eat only 10 oz of charbroiled T-bone every eight months, two slices of bread daily, or 1.5 oz of lettuce daily. Thus, the criteria for PAHs in drinking water are "protective of human health" but highly unrealistic when compared with other environmental and lifestyle exposures.

Other examples of setting the action levels for interviewing exposures include comparisons of the magnitude of the hazard with the potential hazard resulting from breakdown products deriving from water chlorination or fluoridation. Fluoridation is an attempt to enhance dental health, perhaps at the expense of increasing the cumulative insult to the rest of the body. This analogy may be explored in future work.

## 14. WATER CHLORINATION AND ACTION LEVELS

Chlorination of drinking water, introduced in the United States in 1908, has been called the single most important advance in water treatment (NAS 1977). As an adjunct to filtration, chlorination effectively reduces the bacterial content of drinking water to safe levels reproducibly and inexpensively. Epidemiological evidence demonstrates the efficacy of chlorination in reducing dramatically the incidence of diseases such as typhoid fever and cholera whose causal agents are transmitted by the water route.

Addition of chlorine to drinking water results in the formation of the hydrolysis product HOCl, or hypochlorous acid, according the following reaction:

$$Cl_2 + H_2O = HOCl + H^+ + Cl^- \ .$$

Hypochlorous acid in turn dissociates or ionizes to release hypochlorite ion ($OCl^-$) by the following reaction:

$$HOCl = H^+ + OCl^- \ .$$

HOCl and $OCl^-$, also called free residual chlorine, exist in equimolar concentrations at pH 7.5 and 25°C. At higher pH, $OCl^-$ species predominates, and at lower values HOCl becomes the major form of chlorine.

Additionally, chlorination of water may result in the formation of oxidation products deriving from chlorine interaction with organic constituents that may be present naturally in the water. Humic and fulvic acids naturally present in source water may be oxidized and chlorinated to yield trihalomethanes (THMs) and other substances of as yet unknown identity or potential health risks. One such THM is chloroform, a known animal carcinogen. Other products of water chlorination are many and varied. If ammonia is present in water undergoing chlorination, chloramines are formed by substitution or oxidation reactions, liberating such species as $NH_2Cl$ (monochloramine), $NHCl_2$ (dichloramine), and $NCL_3$ (nitrogen trichloride). If bromine is present, the oxidation product HOBr (hypobromous acid) may combine with ammonia (if present) to produce bromamines. The presence of phenols in source water may result in the formation of chlorinated phenols such as 2-chlorophenol, 2,4-dichlorophenol, and 2,4,6-trichlophenol. Data exist which suggest that 2-chlorophenol enhances the tumorigenicity of ethylnitrosourea (Exon 1985). Other by-products of chlorine interactions with organics in water include haloacetonitriles, halogenated ketones and aldehydes, and chlorobenzenes. Adverse health effects of these by-products range from hepatic and renal toxicity to mutagenic, clastogenic, and carcinogenic activity. Clearly, chlorination of drinking water may produce potentially negative health effects deriving from halogenation of organics.

The use of other disinfectants such as ozone and, particularly, $ClO_2$ (chlorine dioxide) that can achieve pathogen reduction without the concomitant production of trihalomethanes (specifically) has been investigated more extensively in recent years. However, chlorination remains the accepted method of water treatment in this country, and whatever risks are involved have been (thus far) tolerated in the context of rendering drinking water "safe" with a reduced ability to transmit communicable disease.

If chlorination of drinking water, then, constitutes an acceptable risk to the majority of the population, perhaps the risk associated with chlorination can be viewed as a reference level by which to assess the relative hazards of exposure to various other commonly encountered pollutants or toxicants. The conceptual difference is that chlorination of water brings a dramatic positive effect to human health perhaps at the potential effect of a small increased risk of chronic or old-age diseases. Thus, for environmental pollutants, a reference standard may be defined at some fraction of the toxicity reference level associated with chlorination of drinking water. Several of these by-products of drinking water chlorination have been scored by the RASH analysis (Jones et al. 1987). Table 13 lists the relative potencies of some representative by-products of drinking water chlorination.

Based on the frequency of distribution of the halomethanes detected in the National Organics Reconnaissance Survey for Halogenated Organics (Symons et al. 1975), the theoretical finished water with the median concentration of each compound would contain about 21 $\mu$g/L of chloroform, 6 $\mu$g/L of bromodichloromethane, 1.2 $\mu$g/L of chlorodibromomethane, and bromoform below the limit of detection of the analytical method used. Application of the harmonic mean formula of Finney for estimating additive joint toxicity of a mixture (Finney 1952) to the evaluation of the relative potency of drinking water as a mixture yields the equation

$$RP_{mix} = \sum_i f_i \bullet RP_i \qquad \text{(Jones et al. 1987).}$$

The relative potency of a mixture is the sum of the fractional relative potencies inherent in the mixture components. In the case of chlorinated drinking water,

$$RP_{dw} = \sum f_i \bullet RP_i$$

$$= \frac{21\ \mu g}{10^9 \mu g}\ CHCl_3\ (0.005) + \frac{6\ \mu g}{10^9 \mu g}\ BrCl_2CH_3\ (0.0065)$$

$$+ \frac{1.2\ \mu g}{10^9 \mu g}\ ClBr_2CH_3\ (0.021)$$

$$= \frac{0.105 + 0.039 + 0.025}{10^9}$$

$$= \frac{.169}{10^9} = 1.7 \times 10^{-10}$$

This calculation estimates the relative potency of drinking water as a function of its content of three trihalomethanes produced directly by the chlorination process. At first glance, the magnitude of $10^{-10}$ factor seems small, but it should be recognized that this factor is for drinking water

**Table 13. RASH scores for representative chlorination by-products relative to B(*a*)P used as a standard**

| Chemical | Relative potency | | |
|---|---|---|---|
| | Median | Low[a] | High[b] |
| Chloroacetic acid | 0.15 | 0.08 | 0.94 |
| Dichloracetic acid | 0.0058 | 0.002 | 0.02 |
| Trichloracetic acid | 0.038 | 0.068 | 0.27 |
| Cyanogen chloride | 0.11 | 0.068 | 0.27 |
| Bromodichloromethane | 0.0065 | 0.001 | 0.052 |
| Trichloronitromethane (Chloropicrin) | 0.10 | 0.025 | 0.13 |
| Tribromomethane (Bromoform) | 0.017 | 0.0035 | 0.23 |
| Chloral hydrate | 0.01 | 0.002 | 0.021 |
| Dichloroacetonitrile | 18.18 | | |
| Bromochloroacetonitrile | 12.99 | | |
| Chloroform | 0.005 | 0.0036 | 0.0065 |
| Dibromochloromethane | 0.021 | 0.0071 | 0.23 |
| 2,4-dichlorophenol | 0.013 | 0.0059 | 0.019 |

[a]Lower bound of interquartile range.
[b]Upper bound of interquartile range.

instead of a chemical contaminant tested in pure form. Toxicological comparisons require an evaluation of the relative potency and the mass of the chemical consumed. Many other halogenated organics detected in finished drinking water are known to derive from the chlorination process, but at present the lack of quantitative data does not permit their incorporation into the drinking water relative potency estimate. The derived value thus represents a conservative estimate of the toxicity of drinking water resulting from chlorination (i.e., the toxicity of water is underestimated) and subsequent risk estimations evolving from comparisons with drinking water as a standard would err on the side of safety (i.e., toxicity of other insults would be overestimated relative to the assessment for chlorination contaminants).

In order to compare the risk of exposure to hazardous chemicals with the risk associated with ingestion of chlorinated drinking water, the following equation can be used:

$$\frac{\text{Risk}_{\text{test}}}{\text{Risk}_{\text{water chlorination}}} = \frac{\text{Concentration}/L_c \times RP_c}{RP_{dw}}, \text{ where } RP_{dw} = 1.7 \times 10^{-10}$$

and concentration/$L_c$ is unitless fractional abundance. Thus, if one knows the RASH-derived relative potency of the interviewing chemical and the concentration per liter (perhaps derived from a chemical analysis), an approximation of its toxicity relative to toxicity deriving from chlorination of drinking water can be made.

## 15. RELATIVE COMPARISONS TO PREVIEW REGULATORY GUIDANCE

For waste management it is important to anticipate forthcoming regulations within the near term (e.g., within five years) and also for the long term for effective postclosure management of hazardous waste sites (e.g., 30 years). The relative potency approach is highly useful for both purposes. Long-range regulations as predicted by RASH comparisons were discussed in Sects. 6 and 8.

Table 2 illustrates chemicals with "infant" or more immature regulatory criteria in that it has traditionally been assumed that these chemicals do not interact to potentiate the effect of carcinogens. Long-range predictions from the RASH analysis are shown for contrast. It is interesting to note the transition of estimates for dichlorobenzenes. This effect is likely to be seen for hundreds of chemicals within the next decade.

Because of the primary goal of this study, it is necessary to use a "risk equivalent" basis to place chemicals and radionuclides on a common scale. It was necessary to modify estimates in column three of Table 13 according to absorption efficiency factors (i.e., absorption coefficients) for ingestion. Radiobiological models are based on doses to the pathological site at risk. In contrast, most hazard models for chemicals are based on concentrations in food, water, or air. Thus, to develop a common scale for hazard evaluation it is important to rank an agent by the magnitude of the response and the dose or concentration that acted at this pathological site. Some chemicals are highly soluble and others are not. Thus, absorption coefficients are needed to evaluate the efficiency of absorption.

The ICRP has recommended absorption coefficients for ingestion of radionuclides (summarized in Appendix D) but no similar data base was found for toxic chemicals. Thus, it was necessary to review biological and pharmacological publications. The newly compiled ORNL data base of absorption coefficients is summarized in Appendix E and will be submitted for journal publication. The data base on absorption coefficients reflects much work and is an advancement beyond what is currently used, even by expert committees. The absorption coefficients described in Appendix E will be expanded to include other ORNL pollutants as they are identified. This risk-based common scale and development of risk coefficients for currently unregulated chemicals are important to soil and pathway exposure studies done in support of RAP projects by other investigators. These applications require absorption coefficients for inhalation and ingestion as presented in Appendix E. Work described in this report is being disseminated into those other activities.

The magnitudes of initial regulations for previously unregulated chemicals have traditionally confused both the regulators and the regulated. Historically, each chemical has been evaluated individually and a permissible concentration established independently of criterion levels set for other chemicals. If the assumption is made that EPA attempts to regulate different chemicals and/or different activities to the same level of hazard by either explicit or implicit considerations, then the relative potency approach of the RASH method permits a rapid and reasonably accurate estimate of the magnitude of "infant" regulations for previously unregulated chemicals.

Infant regulations and even more mature criteria are frequently based on one biological test (e.g., see the EPA Health Assessment Document for

PCBs) and large safety factors (e.g., see Appendix B) and, therefore, are subject to potentially large individual variation. It was decided that such initial projections for currently unregulated chemicals should be based on an ensemble of noncarcinogenic reference chemicals having an abundance of *in vitro* and *in vivo* test data; the chemicals should have experienced significant industrial usage; and the chemicals should have "reference dose" values (i.e., RfD) as published by the EPA (51FR21673). The RfD values were derived by EPA for what the EPA calls noncarcinogens.

Barium, cresol, lead, mercury, pentachlorophenol, phenol, and toluene were taken as benchmarks of reference RfD values. As seen in Table 14, the relative potency from the RASH method was multiplied by the RfD value published by EPA in order to compare the relative magnitudes of the potential hazard for the seven chemicals. The geometric mean was taken so that for any chemical (not currently regulated by RfDs) an estimate of the "infant" regulation can be obtained from equation (1) in Table 14.

Estimates derived by this technique are given in column one of Table 14. It should be noted that these values compare well with EPA-derived values given in various columns of Table 7 for noncarcinogenic chemicals.

**Table 14. "Infant" or EPA-RfD-type interim values for any chemical (i.e., chemical i). $RP_i$ can be derived from the $RfD_i$ as shown in this table. These values can be used as short-term projections for chemicals not currently regulated by EPA.**

| Chemical | EPA-RfD (mg/L) | RASH-RP | Ln (RfD·RP) |
|---|---|---|---|
| Barium | 1.0 | 0.030 | -3.5 |
| Cresol | 2.0 | 0.015 | -3.5 |
| Lead | 0.05 | 0.092 | -5.4 |
| Mercury | 0.0002 | 0.40 | -7.1[a] |
| Pentachlorophenol | 1.0 | 0.11 | -2.2 |
| Phenol | 4.0 | 0.027 | -2.2 |
| Toluene | 10.0 | 0.0038 | -3.3 |
| Mean[b] | | | -3.9 |

[a]Based on this simple relative comparison, it appears that the RfDs for mercury and lead are more cautious than RfDs for other chemicals in this table.

[b]Mean value of (RfD·RP) = exp(-3.9) = 0.02. Hence,

$$RfD_i = \frac{0.02 \text{ mg/L}}{RP_i}$$

## ACKNOWLEDGMENTS

This study was made possible through enthusiastic support from L. W. Barnthouse, J. R. Trabalka, and F. E. Sharples of the Environmental Sciences Division (ORNL), and P. J. Walsh of the Health and Safety Research Division (ORNL). Technical contributions derive from many unlisted collaborators spanning several years. Technical contributions and expert technical reviews were provided by M. D. Morris of the Engineering Physics and Mathematics Division (ORNL) and L. R. Glass of the University of Texas and ORNL Health Effects and Epidemiology Group. K. F. Eckerman and R. W. Leggett provided valuable assistance in the interpretation of risk coefficients for radionuclides. Joe Rich coordinated tasks involving editing, preparation, and reproduction in an effective manner in order to meet the required delivery date. Editorial assistance was provided by Nancy Prince, Tina Sekula, and Sherry Hawthorne. Donna Fisher, Frances Littleton, and Sandi Lyttle provided much expertise and timely support in the preparation of this document and over the entire study period.

## REFERENCES


Ames, B. N., R. Magaw, and L. S. Gold (1987). "Ranking Possible Carcinogenic Hazards." *Science* 236, 271-280.

ACGIH (1987). "Threshold Limit Values and Biological Exposure Indices for 1986-1987." American Conference of Governmental Industrial Hygienists.

Department of Health and Human Services (1985). "Risk Assessment and Risk Management of Toxic Substances," DHHS Committee to Coordinate Environmental and Related Programs. April 1985.

Dourson, M. L., and Stara, J. F. (1983). "Regulatory History and Experimental Support of Uncertainty (Safety) Factors." Regulatory Toxicology and Pharmacology 3, 224-238.

Dourson, M. L. et al. (1985). "Novel Methods for the Estimation of Acceptable Daily Intake," in Advances in Health Risk Assessment for Systemic Toxicants and Chemical Mixtures. Toxicology and Industrial Health (Stara, J. F. and Erdreich, L. S., eds.), Vol. 1, No. 4. Princeton Scientific Publishing Co., Inc. Princeton, N.J., pp. 23-41.

Easterly, C. E., and Glass, L. R. (1987). "Toxicity of Petroleum Products as Predicted with a Relative Potency Methodology." submitted to *J. Pharm. and Applied Toxicology.*

Easterly, C. E. (1987). "Relative Toxication of Agricultural Chemicals Used in Tennessee." (Abstract) presented at the Annual Meeting of the Tennessee Viticultural and Oenological Society, Nashville, TN. Jan 9-10, 1987.

Environmental Protection Agency (EPA) (1984). Proposed Guidelines for Carcinogen Risk Assessment. *Federal Register* 49(227).

Environmental Protection Agency, Environmental Criteria and Assessment Office (1985). "Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs)." PB86-118312, April 1985.

Environmental Protection Agency (1986). "Superfund Public Health Evaluation Manual." Office of Emergency and Remedial Response, Washington, D.C. EPA 540/1-86/060.

Exon, J. H., and Koller, L. D. (1985). "Toxicity of 2-Chlorophenol, 2,4,-Dichlorophenol, and 2,4,6-Trichlorophenol," in Water Chlorination: Chemistry, Environmental Impact and Health Effects, Vol. 5, R. L. Jolley et al., eds. Lewis Publishing, Inc., Chelsea, Michigan. pp. 307-330.

Gaylor, D. W. (1983). "The Use of Safety Factors for Controlling Risk." *J. Toxicology and Env. Health* 11, 329-336.

International Agency for Research on Cancer (1982). "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans." Suppl. 4.

International Commission on Radiological Protection (1980). "Limits for Intakes of Radionuclides by Workers," F. D. Sowery, ed. Publication No. 30. Pergamon Press, New York.

Jackson, B. A. (1980). "Safety Assessment of Drug Residues." *J. Amer. Vet. Med. Assoc.* **176**(10, 1141-1144.

Jones, T. D., G. D. Griffin, and P. J. Walsh (1983). "A Unifying Concept for Carcinogenic Risk Assessments." *J. Theor. Biol.* **105**, 35-61.

Jones, T. D., P. J. Walsh, and E. A. Zeighami (1985). "Permissible concentrations of Chemicals in Air and Water Derived from RTECS Entries: A "RASH" Chemical Scoring System." *Toxicology and Industrial Health* 1(4), 213-234.

Jones, T. D., P. J. Walsh, A. P. Watson, L. W. Barnthouse, and D. A. Sanders (1987). "Chemical Scoring by a Rapid Screening Hazard (RASH) Method." *Risk Analysis*, submitted for publication.

MacMahon, B., and Sugimura, T. (eds.) (1983). "Coffee and Health." Banbury Report 17. Banbury Center Conference held in October 1983. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Munro, N. B., and Travis, C. C. (1986). "Drinking Water Standards." *Environ. Sci. Technol.* 20(8), 768-769.

National Academy of Sciences (1977). "Drinking Water and Health." Safe Drinking Water Committee, National Research Council, National Academy of Sciences, Washington, D.C.

National Council on Radiation Protection and Measurements (1987). "Recommendations on Limits for Exposure to Ionizing Radiation." NCRP Report No. 91. National Council on Radiation in Protection and Measurements, Bethesda, Maryland.

Rodricks, J. V., Brett, S., and Wrenn, G. (1987). "Significant Risk Decisions in Federal Regulatory Agencies." Environ Corporation, Washington, D.C.

Rupp, E. M., Parzyck, D. C., Walsh, P. J., Booth, R. S., Rairdon, R. J., Whitfield, B. L. (1978). "Composite Hazard Index for Assessing Limiting Exposures to Environmental Pollutants: Application Through a Case Study." Environmental Science and Technology 12, 802.

Sittig, M., editor (1980). "Priority Toxic Pollutants: Health Impacts and Allowable Limits." Noyes Data Corp., Park Ridge, New Jersey.

Stokinger, H. E., and Woodward, R. L. (1958). "Toxicologic Methods for Establishing Drinking Water Standards." JAWWA 50(4), 515-529.

Sullivan, T. E., N. S. Nelson, W. H. Ellett, D. E. Dunning Jr., R. W. Leggett, M. G. Yalcintas, and K. F. Eckerman (1981). "Estimates of Health Risk from Exposure to Radioactive Pollutants." ORNL/TM-7745.

Symons, J. M. et al. (1975). "National Organics Reconnaissance Survey for Halogenated Organics." JAWWA 67(11), 634-647.

Travis, C. C. et al. (1987). "Cancer Risk Management. A Review of 132 Federal Regulatory Decisions." *Env. Sci. and Technology* 21, 415.

Walsh, P. J., Kilough, G. G., and Rohwer, P. S. (1978). "Composite Hazard Index for Assessing Limiting Exposures to Environmental Pollutants: Formulation and Derivation." Environmental Science and Technology 12, 799.

# APPENDIX A

## RISK FROM EXPOSURE TO CHROMIUM

(Adopted from information presented in EPA-600/8-83-014F)

Chromium III is considered to be an essential micronutrient at low concentrations because a deficiency causes buildup of glucose in blood. Animal studies have demonstrated that chromium-deficient rodents gain less weight and have shorter life spans than animals maintained on a chromium-adequate diet. In humans, symptoms of chromium deficiency consist of glucose intolerance, weight loss, and confusion. However, as with all other chemicals, high doses of chromium III are toxic.

Chromium VI compounds are more readily absorbed through skin, gut, lung, and biological membranes than are compounds of the trivalent form. Chromium VI is irritating and corrosive and is reduced to chromium III by cellular activities.

The CAG accepted the study by Mancusco (1975) as providing limited but adequate information for estimating the carcinogenic potency of hexavalent chromium. Conditions of the Mancusco study are summarized in Table A.1.

The CAG analysis assumed that the individual worker exposure schedules resulted in equivalent risk as that from a continuous exposure given at a time-weighted average or concentration rate over an equal time frame.

The age-specific incidence was treated as a power function of time according to the model of Druckrey (1967), and lifetime cancer risk in terms of exposure and age took into account competing risks based on the probability of surviving to a specific age.

Numerical coefficients of the risk model were evaluated (based on the assumption that the number of lung cancer deaths at a specific age follows the Poisson distribution) by the method of maximum likelihood.

The CAG risk coefficient is 41 $(mg/kg/d)^{-1}$. For a risk level of $10^{-5}$, the permissible dose would be $(10^{-5}/41)$ (mg/kg/d) (70 kg) = 0.017 $\mu$g/d based on inhalation. If Reference Man (ICRP 23) breathes 20 $m^3$/d, then the permissible concentration would be 0.85 $ng/m^3$.

If the inhalation absorption coefficient of chromium is taken at 0.25, and the oral absorption is 0.05 based on values in Table 1 of Appendix E, then the concentration of chromium in drinking water is (0.017 $\mu$g/d) (0.25/0.05)/(2 L/d) = 0.042 $\mu$g/L.

**Table A.1. Chromium risk (Mancusco 1975)**

| | |
|---|---|
| Exposure period | (1931-1937) to 1974 |
| Follow-up period | Until 1974 |
| Number of subjects | 332 white males in chromate plant |
| Total number of deaths | 35 |
| Level of exposure | <1 to 8 $mg/m^3$/year. TWAs of exposure to insoluble, soluble, and total chromium per cubic meter were calculated for each occupation and for each worker in every department |
| Duration of exposure | ≤43 years |
| Level of risk | In 1949 a comprehensive program was begun to reduce employee exposure, so level of risk decreased accordingly |
| Disease occurrence | Lung cancer |
| Miscellaneous | CAG used only the dose-response data for total chromium to estimate carcinogenic potency of hexavalent chromium. CAG thought this underestimation of the potency of Cr VI was compensated for by other factors that may overestimate risk |
| CAG values | Unit cancer risk 41 $(mg/kg/d)^{-1}$<br>CAG potency index $4 \times 10^3$ |

## APPENDIX B

## TOXICOLOGICAL SAFETY FACTORS AND PRIORITIZATION OF HAZARDS

Interoffice Memorandum

August 14, 1987

M. D. Morris

Uncertainty factors vs safety factors for absolute and relative decision making.

Safety factors vs uncertainty factors? In EPA's toxicology program, these terms have become interchangeable (Dourson and Stara 1983; Dourson et al. 1985). But, it may be timely to remember that statistical uncertainty factors are quite different from the EPA's safety factors. Furthermore, safety factors, uncertainty factors, modifying factors, upper 95% maximum likelihood estimates, unit risk estimates, $Q^*$, RfD, RSD, and RAC as currently defined by the EPA may be used for absolute decision making (i.e., finding an acceptable exposure to one particular chemical), but because the concepts may reflect large and highly variable safety considerations for each chemical, these quantities should not be used to rank chemical hazards, or prioritize chemical sites as reflected by assessment methodologies such as the Hazard Ranking System (HRS) used by EPA to achieve a National Priorities Listing (NPL) for Superfund activities.

Safety factors were devised to estimate a "safe" dose to a hypothesized sensitive human subpopulation when some human or animal dose-response data are available. Particular chemicals have had very limited testing, and a series of simultaneous safety factors and/or modifying factors have been used to ensure protection of human health. For such a chemical, the "permissible exposure" may be safe by a wide but unknown margin. The disadvantage in this absolute decision-making schema is the inconvenience and expense of excessive margins of safety and an inaccurate perception of actual risk. Safety and/or modifying factors have been proposed for:

(1) Intraspecific variability--a factor of 10.
(2) Interspecific variability--a factor of 10.
(3) Subchronic test data when chronic not available--a factor of 10.
(4) Use of LOAEL when NOAEL not available--a factor of 1 to 10.
(5) Test data do not reflect route of exposure for humans--a factor of 10.
(6) Use of acute test data when chronic data not available--a factor of 10.
(7) Qualitative professional judgments regarding scientific uncertainties not covered under the standard uncertainty factors, such as the completeness of the data base for a particular chemical and the number of animals in the key study. These considerations are described as a "modifying factor"--a factor of 1 to 10.

Typically EPA has considered factors (1), (2), (3), and (4) to establish safety factors of 10, 100, 1000, or 5000 for RfD considerations. However, factor number (7) may be used to decrease the RfD by an additional factor of 1 to 10. The modified ADI method described by Mitre (1986) uses safety factors that product to $10^5$.

Although a "possibly safe" dose decreased by safety/modifying factors of 10 to $10^5$ could produce a "more safe" dose, it appears that the derived values impede chemical ranking, site/technology prioritization, and other considerations that depend upon reasonably accurate relative comparisons. A current example is EPA's congressional mandate to regulate 83 contaminants in drinking water by 1989. The original selection of the 83 candidates and EPA's option to substitute seven other chemicals for seven of the 83 can be strongly affected by uncertainty and/or safety factors (e.g., 52FR25726).

The RfD for a particular chemical is computed according to

$$RfD = NOAEL/(S.F.)/(M.F.) \qquad (A)$$

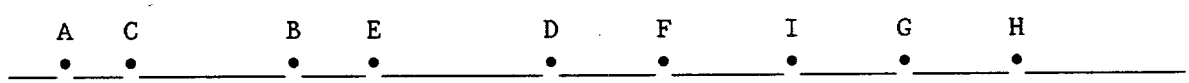
where S.F. is a safety factor of 10, 100, 1000, or 5000 from considerations (1) through (4) and M.F. is from consideration (7). Assume an example of nine chemicals designated A-I. If the NOAEL's for chemicals A-I are compared on a common scale (e.g., mg/kg/day), the following hierarchy may be observed:

Scale I


NOAEL (mg/kg/day)

If other considerations such as relative potency at some particular response level is used to develop the common scale (e.g., $P_{25}$, $P_{50}$, $P_{75}$) then some scrambling of Scale I would be expected--e.g., see Scale II:

Scale II

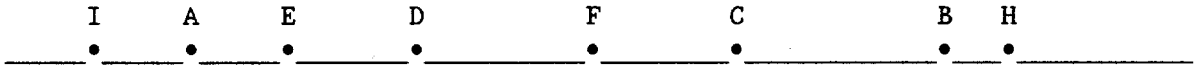



NOAEL (mg/kg/day)

It is unproved whether techniques reflected in Scale I are more suited to risk analysis decisions than techniques reflected in Scale II; but, if these methods are used to categorize risks, then similar decisions may result (Jones et al. 1987).

In contrast, if Scale I is modified by Equation (A), then all relative accuracy may potentially be lost as illustrated by Scale III:

Scale III




Please consider the above concerns and the cited references. Then we should plan a "shirt sleeve" session to evaluate EPA's use of uncertainty/safety factors and whether we should devise a methodology more consistent with relative decision making.

T. J. Jones, 4500S, MS-101 (4-6257)

P. J. Walsh, 4500S, MS-124 (4-5845)

TDJ:dhf

cc: C. E. Easterly
C. S. Gist DOE-ORO
L. R. Glass
A. R. Hawthorne
H. W. Hibbitts DOE-ORO
B. A. Owen
F. E. Sharples
J. R. Trabalka

References Cited

Mitre (1986). Hazard Ranking System Issue Analysis: Toxicity as a Ranking Factor (July). Prepared for the USEPA, Office of Emergency and Remedial Response. The Mitre Corporation, McLean, VA.

Jones, T. D., Walsh, P. J., Watson, A. P., Barnthouse, L. W., and Sanders, D. A. (1987). "Chemical Scoring by a Rapid Screening Hazard (RASH) Method. *Risk Analysis*, in press.

Dourson, M. L., and Stara, J. F. (1983). "Regulatory History and Experimental Support of Uncertainty (Safety) Factors." *Regulatory Toxicology and Pharmacology* **3**, 224-238.

Dourson, M. L., Hertzberg, R. C., Hartung, R., and Blackburn, K. (1985). "Novel Methods for the Estimation of Acceptable Daily Intake." *Toxicology and Industrial Health* **1(4)**, 23-33.

Stokinger, H. E., and Woodward, R. L. (1958). "Toxicologic Methods for Establishing Drinking Water Standards." *J. of American Water Works Association*, 515.

## APPENDIX C

## REVIEW OF RADRISK MODELS FOR RADIONUCLIDES

### Summary of RADRISK Calculations

The RADRISK computer code was developed to estimate dose rates and subsequent health effects to a group of persons due to inhalation or ingestion of a radionuclide (Sullivan et al. 1981). Dosimetry calculations (based on ICRP Publication 30) were coupled with a life-table methodology for evaluating risk based on occupational exposures (Bunger, Cook and Carrick 1981). The dosimetry calculations are used as input data to dose-response models thought to be representative of how a human population may respond to radiation exposure. The dose-response model used by RADRISK is summarized briefly as follows.

The population group at risk in RADRISK is a hypothetical cohort of $10^5$ persons, born simultaneously, and subjected to the same individual competing causes of death throughout life as estimated from the total U.S. population.

Each person was assumed to have lifetime exposure at a constant rate to a unit concentration of each radiochemical. Exposure routes included inhalation, ingestion, immersion in a cloud, and exposure from soil. For water-criteria decisions involving mixed waste, only the fatal cancers derived from intake via the ingestion of radiochemicals will be considered in this document.

In RADRISK, alpha radiation was assumed to be 20-fold more toxic than low-LET beta or photon radiations, on a unit dose basis. Cancers thought to be radiogenic are listed in Table 1 of the Sullivan report. Risk coefficients were derived from the 1972 BEIR report. Excess fatal cancers were computed from absolute and relative risk models. For both models, calculations assumed an initial latency period immediately postexposure. Then, two calculations were made. The first assumed a 30-year plateau, and the second assumed a lifetime plateau for frank expressions of solid cancers--except a 25-year plateau was used for leukemia in all calculations. During this plateau period, risk was assumed to be constant per unit time interval. The plateau assumption is somewhat unrealistic but is necessitated by the lack of biological data. This assumption would have the most profound effect on the days of life lost as computed by RADRISK and should have only a secondary effect on fatal cancers. There would be some effect on the calculated fatal cancers because the life-table analogy for competing risks would continue to reduce the population at risk on an annual basis. These calculations for the two different plateau periods were averaged to derive a risk coefficient of $200 \times 10^{-6}$ fatal cancers per person-rad. The organic-specific estimates in Table 1 of Sullivan were obtained by allotting the $200 \times 10^{-6}$ deaths per person-rad among individual anatomical organs at risk (Sullivan et al. 1981; 51FR34844). Values for bone marrow, bone surface, lung, breast, and thyroid were based on UNSCEAR (1972, 1977) and BEIR (1972, 1980). Risk coefficients for liver, pancreas, stomach, and lower large intestine were derived from UNSCEAR (1977) and draft versions of BEIR III (1980). Sullivan et al. (1981) state that estimates in Table 1 of this report may be uncertain by two-fold, but probably reflect what is currently known about radiogenic cancers in individual organs.

Values for lifetime risk resulting from 1 rad to the liver, pancreas, stomach, and lower large intestine were subtracted from the total body risk from 1 rad, and the residual risk was split equally among the remaining organs listed in Table 1 (Sullivan et al. 1981).

## APPENDIX D

## REVIEW OF ICRP MODELS FOR RADIONUCLIDES

### General

ICRP Publication 30, Part I, presents physical, metabolic, and dosimetric methods used to derive "Limits for Intakes of Radionuclides by Workers." The basic approach is to develop a calculational analogue that simulates uptake of individual radionuclides via inhalation and/or ingestion. Absorption coefficients are used to specify the fraction of the exposure that is transferred from lung or gut to blood. Next, metabolic models are used to predict the distribution of the nuclides to individual organs, their retention in different organs, and elimination through expiration in breath, excretion in urine or feces, etc. A method of specific absorbed fractions is used to account for the fractional energy balance when a source organ irradiates other organs or itself. The ICRP

> intended that these values will be applied at the doses and dose rates of interest . . . using the hypothesis that risks of these effects are linearly related to dose equivalent without threshold. Therefore, the risks of fatal cancer in an individual, group, or population and of hereditary disease in their offspring is determined either by the total dose equivalent received by individuals, independent of dose-equivalent rate and the way dose equivalent is fractionated, or by the collective dose equivalent within the group or population exposed . . . .Several organs and tissues will be irradiated following the entry of a radionuclide into the body . . . must be limited so that the resulting total risk of cancer and hereditary disease is less than or equal to the risk from irradiating the whole body uniformly to the appropriate annual dose-equivalent limit . . . data given here are to be used only within the framework of its basic recommendations as described in ICRP Publication 26. . . . The models used . . . have been chosen, often conservatively, . . . to ensure protection. . . . Data . . . should therefore not be used indiscriminately out of context, e.g., to estimate the risk of cancer in individual cases.

### Dose Equivalent vs Effective Dose

Dose equivalent is calculated by the product of absorbed dose and a quality factor Q. Q is defined as a continuous function of collision stopping power in water. The ICRP and others have traditionally taken $Q = 1$ for beta particles, electron and all electromagnetic radiations including gamma radiation, X rays, and bremsstrahlung; $Q = 10$ for fission neutrons and for protons, and $Q = 20$ for alpha particles, recoil nuclei, and fission fragments.

Dose equivalent is, thus, a purely physically based concept. Frequently, Q is confused with the relatively biological effectiveness (RBE) of different radiations. The magnitude of RBE is determined by several factors, including the pathological effect of interest, the dose level (or response level), the rate at which the dose is delivered, and the

radiation that deposits the dose (e.g., photon or proton). Currently, the ICRP, NCRP, and others are attempting to reconcile some of the discrepancies between quality factors (Qs) and RBEs. Previously, these comparisons have been made for radiation-induced leukemia (Jones 1984), but the issue is far from resolution by NCRP or ICRP. The scope of this project does not permit a more realistic development for RBE or Q considerations in the manner of leukemia (Jones 1984). Thus, in this work, radiations of different effectiveness will be considered according to the traditional Qs (ICRP 30). At high doses, the magnitudes of the RBE values are expected to be approximately near the values of the Q, but it should be recognized that the RBE values at levels of population exposure (i.e., very low doses) may be as much as four-fold greater than currently used Q values (Jones 1984). The RBE concept for ionizing radiations is directly analogous to the relative potency of chemicals as discussed in the main body of this document.

Organ Risk Weighting Factors

For stochastic effects, including cancer, the ICRP proposed to limit exposure on the principle that the magnitude of calculated risk should be equal whether the whole body is irradiated uniformly or whether there is nonuniform radiation.

The mathematical condition used is $EW_T \bullet H_T = H_{wb}$ where $W_T$ is a weighting factor representing the ratio of the stochastic risk resulting from Tissue (T) to the total risk if the whole body is irradiated uniformly, $H_T$ is the dose equivalent to Tissue T, and $H_{wb}$ is the stochastic dose-equivalent limit for uniform whole-body irradiation.

ICRP Publication 26 provides organ risk weighting factors for stochastic risks (i.e., cancer and genetic effects) based on mortality data published in UNSCEAR (1977). Those values have been used widely and are listed in Table D.1.

Again, it is emphasized that an effect is assumed to occur in linear relation to dose equivalent. "Therefore, it is the total dose equivalent averaged throughout any organ or tissue, independently of the time over which that insult is delivered or the gradient of the dose equivalent over the organ at risk" (ICRP 30).

Recently the EPA has proposed to regulate radionuclides in drinking water (EPA 1986). In that proposal, EPA used organ risk weighting factors that the EPA derived from BEIR III (NAS 1982). Those values are shown in Table D.2.

The logical basis for the weighting factors proposed by EPA has not been published, and conceptually the ICRP values are significantly different. Those differences include: ICRP 26 factors are based on UNSCEAR-77 data and EPA factors are based on BEIR III (BEIR III has been a source of major controversy, and it is not known if future NAS-BEIR estimates will accurately track values in BEIR III); ICRP factors are based on mortality, and EPA factors are based on incidence; and ICRP factors include genetic deaths (i.e., $W_T$ for gonads is 0.25); ICRP factors are better documented (ICRP 26) and more widely accepted than the recently proposed EPA factors.

Risk values from ICRP 26 were used to compute anatomical organ risk weighting factors for fatal cancers as shown in column two of Table D.3. ICRP 26 factors and the proposed EPA factors are also shown for comparison.

**Table D.1. Organ risk weighting factors recommended by the ICRP for mortality from cancer and genetic effects**

| Tissue | $W_T$ |
|---|---|
| Gonads | 0.25 |
| Breast | 0.15 |
| Red bone marrow | 0.12 |
| Lung | 0.12 |
| Thyroid | 0.03 |
| Bone surfaces | 0.03 |
| Remainder | 0.30 |

Table D.2. Organ risk weighting factors used by EPA for cancer incidence data from BEIR III

| Organs | Weighting factor |
|---|---|
| Red bone marrow | 0.16 |
| Endosteal bone | 0.009 |
| Thyroid | 0.099 |
| Breast | 0.13 |
| Lung | 0.21 |
| Remainder | 0.392 |

**Table D.3. Comparison of organ risk weighting factors derived from ICRP 26 for cancer mortality with EPA proposed risk factors for cancer incidence**
(Our computations are given in parentheses)

| Tissue | ICRP 26[a] | ICRP[b] | EPA[c] |
|---|---|---|---|
| Gonads | 0.25 | | |
| Breast | 0.15 | (0.20) | 0.13 |
| Red bone marrow | 0.12 | (0.16) | 0.16 |
| Lung | 0.12 | (0.16) | 0.21 |
| Tryroid | 0.03 | (0.04) | 0.099 |
| Bone surfaces | 0.03 | (0.40) | (0.392) |

[a]Values recommended by ICRP 26 based on data in UNSCEAR 1977 and include fatal malignant diseases and genetic defects expressed in liveborn descendants.

[b]ICRP values adjusted to fatal cancers only.

[c]Based on cancer incidence data from NAS BEIR III.

From Table D.3, it seems the uncertainty factor may be as great as four-fold for the most uncertain organ weighting factor (i.e., bone surfaces) although a factor of two is more common for other tissues.

Identification of Target Cells for Cancer

For gastrointestinal tract (GI) cancers, the target cells are assumed to be the mucosal layer; for bone cancer, the bone cells within 10 $\mu$m of the surface; and for skin cancers, the basal layer of the epidermis at a depth of 70 $\mu$m. For other sites, the sensitive cells have not been specified.

The actual proliferating stem cells of the gut and the skin have been identified with reasonable accuracy. Also, bone cells derive from hematopoietically active marrow and migrate to bone surface. There is some uncertainty as to when dose can be effectively delivered, i.e., whether the lesions that initiate bone sarcomas actually derive from endosteal cells on the bone surface, from marrow cells within a few cell diameters of the bone surface, or from both sources. The marrow cells differentiate to become endosteal cells and regenerate bone tissue. Thus, the target cells cannot be identified by theoretical considerations, and one would need complex experimental studies to clarify this issue. Most likely, this source of uncertainty is small and different variables work simultaneously. Some factors, such as the identity of the target cells, could work to decrease dose, but some radiations, for example, tend to give up energy more rapidly at the end of their track length.

The net effect from identification of target cells is impossible to assess at this time, but this application is for intake from drinking water. Hence, the uncertainty in dose and risk models is likely to be small compared with other sources of variability in radiation and chemical dose and risk models. For convenience, we pick this source of uncertainty to be about two from considerations based on ingestion.

Dose Assessment to Target Cells

Some sources of uncertainty were discussed and estimated in the preceding section on "Identification of Target Cells for Cancer." In addition, there is some variability from radioactive decay models, the use of continuous slowing down models for energy deposition along the path of a charged particle, and some "straggling" in direction, especially for low-mass particles such as electrons and betas.

As stated by ICRP 30, reduced effectiveness from nonuniform doses (e.g., "hot particles") has been demonstrated at high doses and high dose rates. However, at low doses and lower dose rates a localized particle could greatly enhance focal proliferation and, thus, could actually be more effective as a local proliferative stimulus to a daughter colony deriving from a "cancer transformed" cell than if the equivalent dose were delivered to the entire organ and its stimulus were averaged over "untransformed" cells.

The ICRP describes variability in the absorbed fraction quantity as being in the range of 1.5x to 2x for dose. Thus, overall variability due to dose assignment is likely to be near 2x.

Dosimetric Model for the Gut

The GI tract model of the ICRP consists of serial transfers through the stomach, the small intestine, the upper large intestine, and the lower large intestine. The small intestine may transfer to body fluids. The lower large intestine eliminates wastes through excretions. Each of the four sections of the gut is assumed to be governed by first-order kinetics. Values of GI absorption coefficients, expressed in terms of percentage transfer are given in Table D.4 for radiochemicals of interest. Radioactive daughters produced in the gut are assumed to have the same transfer coefficient as the appropriate stable isotope. When the value is 100%, all absorption takes place in the stomach. Individual members of a human population may have markedly different absorption characteristics due to physiological and lifestyle factors. Those variations plus the uncertainties in Table D.5 suggest that the overall variability is unlikely to be less than a factor of ten. This estimate is for an incomplete listing of the factors contributing to statistical uncertainty. A more complete listing would likely suggest a potential uncertainty of no less than 20-fold. This estimate is strikingly larger than the value of four or five published by EPA (51FR34844).

Table D.4. Absorption coefficients for ingestion of radiochemicals from ICRP Publication 30

| Radionuclide | Oral absorption (%) | Range (%) | Comments |
|---|---|---|---|
| Tritiated water | 100 | | Assumed to be completely and instantaneously absorbed; mixes rapidly with total body water |
| Cobalt | 30 | | Organically complexed compounds and most inorganic compounds |
| | 5 | | Oxides and hydroxides and inorganic compounds ingested in tracer quantities |
| Strontium | 30 | 20-50 | Soluble salts |
| | 1 | | $SrTiO_3$ |
| Cesium | 100 | | Most compounds are rapidly and almost completely absorbed |
| Thorium | 0.02 | 0.01-0.06 | 0.5 to 1% for 232-$Th(NO_3)_4$ for rat; 0.01-0.06% for 234$Th(SO_4)_2$ mock radium dial paint |
| Uranium | 5 | 0.5-5 | Water-soluble inorganic compounds of hexavalent; uranyl nitrate hexahydrate in man |
| | 0.2 | <1 | For relatively insoluble compounds (e.g., $UF_4$, $UO_2$, and $U_3O_8$) in which U is tetravalent |
| Plutonium | 0.001 | | Oxides and hydroxides |
| | 0.01 | | All other commonly occurring compounds (much higher absorption has been reported for citrates, hexavalent compounds, and other inorganic complexes) |
| Americium | 0.05 | 0.01-0.14 | Studies in rats (greater absorption might be expected for complexed forms) |
| Curium | 0.05 | 0.003-0.07 | Studies in rats (greater absorption might be expected for complexed forms) |
| Technetium | 80 | 50-90 | Pertechnetate in man = 95%, but subject to erratic absorption with marked variability; technetium chloride in rats = 50%) |
| Europium | 0.10 | 0.02-0.3 | Europium chloride in rats |

**Table D.5. Potential uncertainty factors for risk from ingestion of radionuclides**

| Condition contributing to uncertainty | Potential magnitude[a] |
|---|---|
| Assignment of organ risk weight factors | ±2X |
| Q vs RBE at population doses | -4X |
| Identification of target cells | ±2X |
| Dose assessment to target cells | ±2X |
| Absorption coefficients and human variability | ±10X |
| Dose-rate effect on disease (NCRP Report 64) | +5X |

[a]Factors assigned as negative would imply that actual risk could be higher than model estimates. The converse would be expected for factors assigned positive values. Random uncertainty is suggested by ±.

DRAFT

# APPENDIX E

## LITERATURE-DERIVED ABSORPTION COEFFICIENT ESTIMATES FOR 21 CHEMICALS VIA ORAL AND INHALATION ROUTES OF EXPOSURE*

Bruce A. Owen

Health and Safety Research Division
Oak Ridge National Laboratory
P.O. Box X
Oak Ridge, TN 37831-6101

Short title: Absorption Coefficient Estimates for 21 Chemicals

*Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC-05-84OR21400 with Martin Marietta Energy Systems, Inc.

ABSTRACT

Knowledge of the absorption efficiency of a chemical via a particular route of exposure is valuable in estimating the risk from exposure to potentially hazardous chemicals. Efficiency of absorption is expressed as an absorption coefficient and generally varies with the route of exposure. Estimates of the oral and inhalation absorption coefficients for 21 chemicals are presented. The literature citations pertinent to the derivation of each estimate are given, as are comments on the rationale for choosing each estimate.

Accurate assessment of the health effects of environmental and/or occupational exposure to potentially hazardous chemicals necessarily employs estimates of the magnitude of exposure to the chemical of interest. Typically, the calculated dose is modified by various conversion factors to reflect the duration of exposure, degree of uncertainty associated with certain extrapolations, or efficiency of absorption of the chemical by specific routes of exposure (commonly ingestion, inhalation, and dermal). The latter factors are termed absorption coefficients and express the fractional or percentage uptake of the chemical into the blood of the exposed individual.

Absorption coefficients are currently used by various occupational health researchers in derivation of estimates of risk. The drinking water criteria documents produced by the EPA contain absorption coefficients in calculations of acceptable daily intake (ADI) and health advisory (HA) indices. ICRP Publication 30 (Limits for Intakes of Radionuclides by Workers) uses absorption coefficients in calculating risks of exposure to radionuclides. Apart from these sources, however, general availability of absorption coefficients, as such, is limited; however, their future utilization is likely to increase in the context of more vigorous regulatory activity. This manuscript is offered in an attempt to improve access by health effects researchers to absorption coefficients for 21 chemicals for both oral and inhalation routes of exposure.

The absorption coefficients presented here are the product of extensive investigation of the biological, toxicological, and pharmacological literature. Three data bases--TOXLINE, the Hazardous Substance Data Base (HSDB), and the Chemical Information Service (CIS)--were consulted, as well as various EPA, ICRP, and National Institute of Occupational Safety and Health (NIOSH) publications, reference texts, serials, and some 175 articles from 25 journals.

It is acknowledged that absorption efficiency is influenced by age, species, dietary and metabolic status, exposure duration, and other situational considerations (Klaassen 1980). The estimates given here, however, are intended to reflect absorption in general by the average human adult. Additionally, wherever possible, data from human studies received greater consideration than animal data in derivation of the values.

Table E.1 contains oral and inhalation absorption coefficient estimates for 21 chemicals. The range of values discovered in the literature is given where appropriate. The references given for each chemical specify the literature evaluated in derivation of the estimates. Following the table are comments on the rationale for choosing each value.

Table E.1. Absorption coefficient estimates derived from the literature cited

| Chemical | Absorption coefficient | | References |
|---|---|---|---|
| | Oral (range) | Inhalation (range) | |
| Barium | 0.10 (0.01-0.85) | 0.75 (0.10-0.75) | 1,2,3,4 |
| Benzene | 1.00 (0.40-1.00) | 0.47 (0.28-0.60) | 4,5,6,7,8,52,69 |
| Benzo(a)pyrene | 0.50 (0.43-0.58) | 0.29 | 9,10 |
| Chlorine | 1.00 (0.90-1.00) | 1.00 | 68,73 |
| Chloroform | 1.00 (0.50-1.00) | 0.63 (0.50-0.77) | 11,12,53 |
| Cresol | 1.00 | 1.00 | 13 |
| Chromium III | 0.01 (0.005-0.18) | 0.10 (0.05-0.10) | 14,15,16,54,69,74,82 |
| Chromium VI | 0.05 (0.02-0.10) | 0.25 (0.10-0.75) | 15,17,18 |
| Dimethylnitrosamine | 0.98 | - | 46,47 |
| Ethylbenzene | 0.90 (0.72-0.92) | 0.64 | 19,55,62 |
| Fluoride | 1.00 (0.80-1.00) | 1.00 | 4,51,75 |
| Lead | 0.10 (0.01-0.65) | 0.50 (0.20-0.62) | 21,22,23,24,25,26,27,70,76,80,81,90 |
| Mercury, elemental | 0.0001 (0.0001-0.045) | 0.75 (0.50-1.00) | 28,29,30,31,77,78,83,88 |
| Mercury, inorganic | 0.15 (0.02-0.15) | 0.02 (0.00-0.85) | 32,33,34,71,77,78,83,88,89 |
| Mercury, organic | 0.95 (0.40-1.00) | 1.00 | 28,34,35,36,37,77,78,83,88,89 |
| Methylene chloride | 1.00 | 0.50 (0.50-0.75) | 38,56,63 |
| Naphthalene | 1.00 | - | 9 |
| Nickel | 0.05 (0.01-0.10) | 0.75 (0.70-0.75) | 13,20,57,64,72,84,85 |
| PCBs | 0.95 | - | 39,48,49,50,58,59,65 |
| Toluene | 1.00 (0.74-1.00) | 0.50 (0.37-0.70) | 8,19,40,42,43,44,60,79,86,87 |
| Xylene | 1.00 | 0.64 (0.54-0.68) | 41,42,45,61,66 |

## COMMENTS ON THE RATIONALE FOR CHOOSING THE ESTIMATES

### Barium

Oral: Although oral absorption of barium varies widely according to age, dietary factors, etc. (EPA 1985), the value chosen reflects the EPA drinking water criteria document value for adult absorption (0.07-0.20) modified by the ICRP 23 and ICRP 30 values (0.01-0.15 and 0.10, respectively). No definitive study of barium absorption in humans has been done (EPA 1985).

Inhalation: The value chosen for inhalation absorption is supported by valid animal experimental data (Cuddihy 1974) and agrees with the majority of values found in the scientific literature.

### Benzene

Oral: The oral absorption value chosen is derived from valid animal experimental data (oral intubation of rabbits with radiolabeled benzene) (Parke 1953). All of the dose was either metabolized or exhaled unchanged, implying virtually complete absorption by this route.

Inhalation: The inhalation value is derived from several human studies of uptake and excretion (Nomiyana 1974, Hunter 1966, Srbova 1950) and is supported by general agreement of literature values.

### Benzo(a)pyrene [B(a)P]

Oral: Quantitative absorption data for orally administered B(*a*)P is scarce, but fecal recovery data (Chang 1943) suggest ~50% oral absorption.

Inhalation: Data specific to inhalation of B(*a*)P were not located in the literature. The value presented here is based upon particle size, adsorption, and respiratory deposition models (Natusch 1974) that address exposure to B(*a*)P as a product of high-temperature combustion.

### Chlorine

Oral: The oral absorption value is based upon ICRP 23 and ICRP 30 references to a human study of excretion of orally administered chlorine (Burrill 1945). Other data derived from appropriate studies were not located in the literature.

Inhalation: The inhalation value is derived from ICRP 30. Other suitable data were not located.

### Chloroform

Oral: The oral absorption value is based upon valid human experimental data from a study of orally administered radiolabeled chloroform (Fry 1972). Virtually all of the dose was accounted for in expired air as either the $CO_2$ metabolite or unchanged chloroform.

Inhalation: The inhalation absorption value was derived from appropriate human experimental data (Lehmann 1910).

Cresol

Specific quantitative data on oral and inhalation absorption of cresol in humans were not found in the literature. The values chosen reflect the similarity of cresol to phenol, as noted in the NIOSH 78-133 criteria document.

Chromium III

Oral: An exact value for oral absorption of chromium cannot be given (NAS 1974). The value chosen is representative of the range of values specified in the majority of literature quotations and seems appropriate here. The low value reflects the relative insolubility of trivalent chromium and its inability to cross biological membranes.

Inhalation: The inhalation value is chosen on the basis of experimental data referred to in ICRP 30. Absorption of inhaled trivalent chromium is a function of particle size and solubility of retained chromium (EPA 1984).

Chromium VI

Oral: The oral absorption estimate is representative of the range of values discovered in the literature. That this value is somewhat higher than the corresponding chromium III value is due to the increased solubility of chromium VI and its ability to cross biological membranes (EPA 1985). The value chosen is supported by valid human experimental data (Donaldson 1966).

Inhalation: The value chosen is based upon inference from valid animal experimental data (Baetjer 1959) specifying at least 25% distribution of dose to blood and tissue following intratracheal administration.

Dimethylnitrosamine

Oral: This value was derived from valid animal experimental data from excretion studies of radiolabeled dimethylnitrosamine (DMNA) in rats (Gomez 1977) and unlabeled DMNA in mice (Magee 1956).

Inhalation: Appropriate inhalation data were not discovered in the scientific literature.

Ethylbenzene

Oral: The oral absorption value is based upon excretion studies of orally administered ethylbenzene in rats (El Masry 1956). No suitable human data were discovered in the literature.

Inhalation: The inhalation value derives from valid human experimental data referenced in the EPA health advisory and drinking water criteria document (Bardodej 1970). Other human inhalation absorption data were not

located in the literature.

Fluoride

The oral and inhalation values were chosen due to general agreement of literature values and are based upon valid human experimental data (WHO 1970).

Lead

The oral and inhalation values given are representative of the ranges of values described in the literature and are based on appropriate human data (Rabinowitz 1974, 1977; Kehoe 1960).

Mercury--elemental

Oral: The value given here reflects the general agreement of low values quoted in the scientific literature.

Inhalation: The inhalation value is based upon valid human experimental data (Kudsk 1965) and agrees with most estimates in the literature of inhalation absorption of mercury vapor.

Mercury--inorganic salts

Oral: The value chosen derives from valid human and animal experimental data (Rahola 1971, Miettinen 1971) and is supported by general agreement of literature values.

Inhalation: Few values for inhalation absorption of inorganic mercury salts were located in the literature. The estimate here seems to be appropriate given the available data.

Mercury--organic

The great preponderance of animal and human data suggest the virtually complete absorption of organic mercury by both oral and inhalation routes of exposure (Junghans 1983, Clarkson 1972, ICRP 1980).

Methylene chloride

Oral: The oral absorption value is based upon the only appropriate estimate found in the literature (McKenna 1981).

Inhalation: This value was chosen due to general agreement of the literature values located (Astrand 1975; IARC 1982; NRC 1978).

Naphthalene

Oral: The oral value is an estimate based upon fecal recovery data suggesting the nearly complete oral absorption of naphthalene (Chang 1943). Other appropriate studies were not located in the literature.

Nickel

Oral: The oral absorption value was chosen due to the general agreement of literature values and is supported by valid human and animal experimental data (EPA 1985, ICRP 1975).

Inhalation: The few estimates of inhalation absorption of nickel (IARC 1982, NAS 1975) were in general agreement and form the basis of the value presented here.

Polychlorinated biphenyls (PCBs)

Oral: The oral absorption value derives from valid animal experimental data (Allen 1974, Albro 1972) and agrees with the majority of literature values located.

Inhalation: No specific references to inhalation absorption of PCBs were located in the literature.

Toluene

Oral: Rabbit studies (Smith 1954, El Masry 1956) indicate that up to 80% of an oral dose of toluene can be accounted for as eliminated metabolites, with the remainder of the dose exhaled unchanged. As discussed in the EPA criteria document (EPA 1985), these data imply greater than 99% absorption from the gastrointestinal tract. Thus, the value given here seems to be a reasonable estimate.

Inhalation: The inhalation absorption value given here is representative of the ranges and values discovered in the literature and is based upon appropriate human and animal experimental data (EPA 1985, Nomiyama 1978).

Xylene--meta-, ortho-, and para- isomers

Oral: The oral absorption value is derived by inference from limited excretion data (Bray 1949) specifying 85 to 90% recovery of an oral dose as urinary metabolites, with pulmonary excretion accounting for the remainder of the dose.

Inhalation: The inhalation value is based upon the majority of human and experimental data suggesting 64% absorption of inhaled xylene (EPA 1985, Sedivec 1976).

References for Table E.1

1. EPA (1985). Drinking Water Criteria Document for Barium, p. III-1. PB86-118031.

2. International Commission on Radiological Protection (1975). Report of the Task Group on Reference Man. ICRP Publication No. 23, p. 370. Pergamon Press, New York.

3. International Commission on Radiological Protection (1980). Limits for Intakes of Radionuclides by Workers. ICRP Publication No. 30, Part 2, p. 48. Pergamon Press, New York.

4. Stokinger, H.E., and Woodward, R.L. (1958). Toxicologic methods for establishing drinking water standards. *J. Am. Water Works Assoc.* 50(4): 515-529.

5. Snyder, R., et al. (1981). Biochemical toxicology of benzene. In *Reviews in Biochemical Toxicology 3* (Hodgson, E., Bend, J., and Philpot, R., eds.), pp. 128-129. Elsevier-North Holland, New York.

6. International Association for Research on Cancer (1974). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Volume 7, Some antithyroid and related substances, nitrofurans and industrial chemicals, p. 211. World Health Organization, Geneva, Switzerland.

7. National Institute for Occupational Safety and Health (1974). Criteria for a Recommended Standard . . . Occupational Exposure to Benzene. HEW Publication No. 74-137 (NIOSH). U.S. Government Printing Office, Washington, D.C.

8. deBruin, A. (1976). Biochemical Toxicology of Environmental Agents (deBruin, A., ed.). Elsevier Scientific Publications, New York.

9. Chang, L.H. (1943). The fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biological Chemistry* 151: 93.

10. Natusch, D.S., and Wallace, J.R. (1974). Urban aerosol toxicity: the influence of particle size. *Science* 186: 695.

11. Fry, B.J., Taylor, T., and Hathaway, D.E. (1972). Pulmonary elimination of chloroform and its metabolites in man. *Arch. int. Pharmacodyn.* 196: 98-111.

12. NRC (1978). Chloroform, Carbon Tetrachloride and Other Halomethanes: An Environmental Assessment (National Research Council Panel on Low Molecular-Weight Halogenated Hydrocarbons), p. 2. National Academy of Sciences, Washington, D.C.

13. Kingbury, G.L., and Chessin, R.L. (1983). Monitoring Trigger Levels for Process Characterization Studies. Project Summary. U.S.

Environmental Protection Agency, Research Triangle Park, NC, November 1983.

14. Toxicology and Biological Monitoring of Metals in Humans (Carson, B.L., Ellis, H.V., III, and McCann, J.L., eds.), p. 70. Lewis Publishers, Chelsea, Michigan, 1986.

15. EPA (1984). Health Assessment Document for Chromium. August 1984. EPA 600/8-87-014F.

16. Rondia, D. (1979). Sources, modes and levels of human exposure to chromium and nickel. In *Trace Metals: Exposure and Health Effects* (DiFerrante, E., ed.), p. 119. Pergamon Press, New York.

17. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 11-1, September 1985, PB86-118338.

18. Donaldson, R.M., and Barreras, R.F. (1966). Intestinal absorption of trace quantities of chromium. *J. Lab. and Clin. Med.* 68: 484.

19. El Masry, A.M., Smith, J.N., and Williams, R. T. (1956). Studies in Detoxication 69. The metabolism of alkylbenzenes: n-propylbenzene and n-butylbenzene with further observations on ethylbenzene. *Biochem. J.* 64: 50-56.

20. *Mutagenicity, Carcinogenicity and Teratogenicity of Industrial Pollutants* (Kirsch-Volders, M., ed.), p. 95. Plenum Press, New York, 1984.

21. Kehoe, R.A., Thamann, F., and Cholak, J. (1933). On the normal absorption and excretion of lead. *J. Ind. Hyg.* XV: 257.

22. Rabinowitz, M.B., and Kopple, J.D. (1974). Lead metabolism in the normal human: stable isotope studies. *Science* 182: 725-727.

23. Rabinowitz, M.B., Wetherill, G.W., and Kopple, J.D. (1976). Kinetic analysis of lead metabolism in healthy humans. *J. Clin. Invest.* 58: 260-270.

24. Klaassen, C.D. (1980). Casarett and Doull's Toxicology. The Basic Science of Poisons (Doull, J., Klaassen, C.D., and Amdur, M. O., eds.), p. 32. Macmillan Publishing Co., Inc., New York.

25. The Pharmacological Basis of Therpeutics, 5th Edition (Goodman, L.S. and Gilman, A., eds.), p. 938. Macmillan Publishing Co., Inc., New York, 1975.

26. Rabinowitz, M.B., Wetherill, G.W., and Kopple, J.D. (1977). Magnitude of lead intake from respiration by normal man. *J. Lab. Clin. Med.* 90: 238-248.

27. Hursh, J.B. and Mercer, T.T. (1970). Measurement of $^{212}Pb$ loss rate from human lungs. *J. Applied Physics* 28: 268.

28. Reuhl, K.R., and Pounds, J.G. (1981). Absorption and disposition of $^{203}Hg$ in the pregnant and nonpregnant hamster following oral administration of [$^{203}Hg$] methylmercuric chloride. *Env. Research* 24: 131-139.

29. Hayes, A.D. and Rothstein, A. (1962). The metabolism of inhaled mercury vapor in the rat studied by isotope techniques. *J. Pharm. Exp. Ther.* 138: 1-10.

30. Kudsk, F.N. (1965). Absorption of mercury vapor from the respiratory tract of man. *Acta Pharmacol. et. Toxicol.* 23: 250-262.

31. Friberg, L.T., et al. (1969). Maximum allowable concentrations of mercury compounds. *Arch. Environ. Health* 19: 891-905.

32. Prickett, C., Laug, E., and Kunze, F. (1950). Distribution of mercury in rats following oral and intravenous administration of mercuric acetate and phenylmercuric acetate. In *Proc. Soc. Exp. Biol. Med.* 73: 585-588.

33. Nelson, N., et al. (1971). Hazards of mercury: special report to the secretary's pesticide advisory committee, Dept. of Health, Education, and Welfare. *Env. Research* 4: 1.

34. Clarkson, T.W. (1972). Recent advances in the toxicity of mercury with emphasis on the alkylmercurials. In *Critical Reviews in Toxicology*, Vol. 1, issue 1, pp. 203-234. CRC Press, Cleveland, Ohio.

35. Junghaw, R.P. (1983). A review of the toxicity of methylmercury compounds with application to occupational exposures associated with laboratory uses. *Environ. Research* 31: 1-31.

36. Aberg, B., et al. (1969). Metabolism of methyl mercury ($^{203}Hg$) compounds in man. *Arch. Environ. Health* 19: 478-484.

37. Berlin, M., Carlson, J., and Norseth, T. (1975). Dose-dependence of methylmercury metabolism. *Arch. Environ. Health* 30: 307-313.

38. Astrand, I. (1975). Uptake of solvents in the blood and tissues of man: a review. *Scand. J. Work Environ. Health* 1: 199.

39. Van Miller, J.P., Hsu, I.C., and Allen, J.R. (1975). Distribution and metabolism of $^{3}H$-2,5,2',5'-tetrachlorobiphenyl in rats. In *Proc. Soc. Exp. Biol. and Med.* 148: 682-687.

40. Smith, J.N., Smithies, R.H. and Williams, R.T. (1954). Studies in detoxication 55. The metabolism of alkylbenzenes. a) glucuronic acid excretion following the administration of alkylbenzenes, b) elimination of toluene in the expired air of rabbits. *Biochem. J.* 56: 317-320.

41. Sandmeyer, E.E. (1978). Aromatic hydrocarbons. In Patty's Industrial Hygiene and Toxicology, 3rd revised ed., vol. 2B (Clayton, C.D., and

Clayton, F.E., eds.), p. 3296. John Wiley and Sons, New York.

42. Wallen, M., Holm. S., and Nordqvist, M.B. (1985). Coexposure to toluene and p-xylene in man: Uptake and elimination. *Brit. J. Ind. Med.* 42: 111-116.

43. Ovrum, P., Hultengren, M., and Lindqvist, T. (1978). Exposure to toluene in a photogravure plant. Concentration in ambient air and uptake in the body. *Scand. J. Work. Environ. Health* 4: 237-245.

44. Nomiyana, K., and Nomiyana, H. (1978). Three fatal cases of thinner-sniffing, and experimental exposure to toluene in humans and animals. *Int. Arch. Occup. Environ. Health* 41: 55-64.

45. Riihimaki, V., Pirkko, P., Savolainen, K., and Pekari, K. (1979). Kinetics of m-xylene in man. General features of absorption, distribution, biotransformation, and excretion in repetitive inhalation exposure. *Scand. J. Work. Environ. Health* 5: 217-231.

46. Magee, P.N. (1956). Toxic liver damage. The metabolism of dimethylnitrosamine. *Biochem. J.* 64: 672-682.

47. Gomez, M.I.D., Swann, P., and Magee., P.N. (1977). The absorption and metabolism in rats of small oral doses of dimethylnitrosamine in human food. *Biochem. J.* 164: 497-500.

48. Goto, M., Sugiura, K., Hattori, M., Miyagawa, T., and Okamura, M. (1974). Metabolism of 2,3-dichlorobiphenyl-$^{14}C$ and 2,4,6-trichlorobiphenyl-$^{14}C$ in the rat. *Chemosphere* 5: 227-232.

49. Goto, M., Sugiura, K., Hattori. M., Miyagawa, T., and Okamura, M. (1974). Metabolism of 2,3,5,6-tetrachlorobiphenyl-$^{14}C$ and 2,3,4,5,6-pentachlorobiphenyl-$^{14}C$ in the rat. *Chemosphere* 5: 233-238.

50. Albro, P.W., and Fishbein, L. (1972). Intestinal absorption of polychlorinated biphenyls in rats. *Bull. Environ. Contam. Toxicol* 8(1): 26-31.

51. Cremer, H-D., and Buttner, W. (1970). Absorption of fluorides. In Fluorides and Human Health.. World Health Organization, Geneva, Switzerland.

52. EPA (1985). Drinking Water Criteria Document for Benzene. PB86-118122.

53. National Institute of Occupational Safety and Health (1974). Criteria for a Recommended Standard - Occupational Exposure to Chloroform. NIOSH 75-114. U.S. Government Printing Office, Washington, D.C.

54. EPA (1985). *Drinking Water Criteria Document for Chromium*, p. III-1. PB86-118072.

55. EPA (1985). *Drinking Water Criteria Document for Ethylbenzene*, p. III-1. PB86-117835.

56. International Association for Research for Cancer (1979). *IARC Monographs on the Carcinogenic Risk of Chemicals to Man*, Vol. 20. Some Halogenated Hydrocarbons, p. 458. World Health Organization, Geneva, Switzerland.

57. EPA (1985). *Drinking Water Criteria Document for Nickel, p. III-4. PB86-117801.*

*58. EPA (1985). Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs)*, p. III-1. PN86-118312.

59. International Association for Research on Cancer (1978). *IARC Monographs on the Carcinogenic Risk of Chemicals to Man*, vol. 18. Polychlorinated Biphenyls and Polybrominated Biphenyls. World Health Organization, Geneva, Switzerland.

60. EPA (1985). *Drinking Water Criteria Document for Toluene*, p. III-1. PB86-117975.

61. EPA (1985). *Drinking Water Criteria Document for Xylenes*, p. III-1. PB86-117942.

62. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 26-3, September 1985. PB86-118338.

63. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 20-3, September 1985. PB86-118338.

64. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 37-3, September 1985. PB86-118338.

65. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 40-3, September 1985. PB86-118338.

66. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 51-3, September 1985. PB86-118338.

67. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 5-4, September 1985. PB86-118338.

68. International Commission on Radiological Protection (1975). *Report of the Task Group on Reference Man*. ICRP Publication No. 23, p. 378. Pergamon Press, New York.

69. International Commission on Radiological Protection (1975). *Report of the Task Group on Reference Man*. ICRP Publication No. 23, p. 380. Pergamon Press, New York.

70. International Commission on Radiological Protection (1975). *Report of the Task Group on Reference Man*. ICRP Publication No. 23, p. 390. Pergamon Press, New York.

71. International Commission on Radiological Protection (1975). *Report of the Task Group on Reference Man*. ICRP Publication No. 23, p. 394. Pergamon Press, New York.

72. International Commission on Radiological Protection (1975). *Report of the Task Group on Reference Man*. ICRP Publication No. 23, p. 397. Pergamon Press, New York.

73. International Commission on Radiological Protection (1980). *Limits for Intakes of Radionuclides by Workers*. ICRP Publication No. 30, part 2, p. 8. Pergamon Press, New York.

74. International Commission on Radiological Protection (1980). *Limits for Intakes of Radionuclides by Workers*. ICRP Publication No. 30, part 2, p. 15. Pergamon Press, New York.

75. International Commission on Radiological Protection (1980). *Limits or Intakes of Radionuclides by Workers*. ICRP Publication No. 30, part 2, p. 1. Pergamon Press, New York.

76. International Commission on Radiological Protection (1980). *Limits for Intakes of Radionuclides by Workers*. ICRP Publication No. 30, part 2, p. 64. Pergamon Press, New York.

77. International Commission on Radiological Protection (1980). *Limits for Intakes of Radionuclides by Workers*. ICRP Publication No. 30, part 2, p. 59. Pergamon Press, New York.

78. EPA (1985). *Drinking Water Criteria Document for Mercury*, p. III-1. PB86-117827.

79. Nomiyama, K., and Nomiyama, H. (1974). Respiratory elimination of organic solvents in man. Benzene, Toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int. Arch. Arbeitsmed*. 32: 85.

80. Carson, B.L., et al. (1986). *Toxicology and Biological Monitoring of Metals in Humans* (Carson, B.L., Ellis III, H.V., and McCann, J.L., eds.), p. 129. Lewis Publishers, Chelsea, Michigan.

81. Mutagenicity, Carcinogenicity and Teratogenicity of Industrial Pollutants (Kirsch-Volders, M., ed.), p. 83. Plenum Press, New York, 1984.

82. Mutagenicity, Carcinogenicity and Teratogenicity of Industrial Pollutants (Kirsch-Volders, M., ed.), p. 78. Plenum Press, New York, 1984.

83. Hammond, P.B., and Beliles, R.P. (1980). Casarett and Doull's Toxicology. *The Basic Science of Poisons* (Doull, J., Klaassen, C.D., and Amdur, M.O., eds.), p. 422. Macmillan Publishing Co., Inc., New York.

84. Carson, B.L., et al. (1986). Toxicology and Biological Monitoring of Metals in Humans (Carson, B.L., Ellis III. H.V., and McCann. J.L., eds.), p. 119. Lewis Publishers, Chelsea, Michigan.

85. International Association for Research on Cancer (1973). *IARC Monographs on the Carcinogenic Risk of Chemicals to Man, vol. 2. Some Inorganic and Organometallic Compounds*, p. 142. World Health Organization, Geneva, Switzerland.

86. EPA (1985). *Health Advisories for 52 Chemicals Which Have Been Detected in Drinking Water*, p. 45-3 (toluene), September 1985. PB86-118338.

87. Fassett, D.W., et al. (1963). *Patty's Industrial Hygiene and Toxicology*, second revised edition, vol. II. Toxicology (Patty, F.A., ed.), p. 1229. Interscience Publishers, New York.

88. Butler, G.C. (1979). Exposure to mercury. In *Trace Metals: Exposure and Health Effects* (DiFerrante, E., ed.), p. 67. Pergamon Press, New York.

89. *Toxicology of Trace Elements*, vol. 2 (Goyer, R.A., and Mehlman, M.A., eds.), p. 3. John Wiley and Sons, New York, 1977.

90. *Toxicology of Trace Elements*, vol. 2 (Goyer, R.A., and Mehlman, M.A., eds.), p. 46. John Wiley and Sons, New York, 1977.

## References for Appendix E


Albro, P.W. and Fishbein, L. (1972). Intestinal absorption of polychlorinated biphenyls in rats. *Bull. Environ. Contam. Toxicol.* 8(1): 26.

Allen, J.R., Norback, D.H. and Hsu, I.C. (1974). Tissue modifications in monkeys as related to absorption, distribution, and excretion of polychlorinated biphenyls. *Arch. Environ. Contam.* 2(1): 86.

Astrand, I. (1975). Uptake of solvents in the blood and tissues of man: a review. *Scand. J. Work Environ. Health* 1: 199-218.

Baetjer, A.M., Damron, C. and Budacz, V. (1959). The distribution and retention of chromium in man and animals. *Arch. Ind. Health* 20: 136-150.

Bardodej, Z., and Bardodejova, E. (1970). Biotransformation of ethylbenzene, styrene, and alpha-methylstyrene in man. *Am. Ind. Hyg. Assoc. J.* 31(2): 206-209.

Bray, H.G., Humphris, B.G., and Thorpe, W.V. (1949). Metabolism of derivatives of toluene 3. o-, m- and p-xylenes. *Biochem J.* 45(1): 241.

Burrill, M.W., Freeman, S., and Ivey, A.C. (1945). Sodium, potassium, and chloride excretion of human subjects exposed to a simulated altitude of eighteen thousand feet. *J. Biol. Chem.* 157: 297-302.

Chang, L.H. (1943). The fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biol. Chem.* 151: 93.

Clarkson, T.W. (1972). Recent advances in the toxicology of mercury with emphasis on the alkylmercurials. In *Critical Reviews in Toxicology*, Vol. 1, Issue 1, pp. 203-234, CRC Press, Cleveland, Ohio.

Cuddihy, R.G. and Griffith, W.C. (1974). A biological model describing tissue distribution and whole-body retention of barium and lanthanum in beagle dogs after inhalation and gavage. *Health Physics* 23: 621-623.

Donaldson, R.M., Jr., and Barreras, R.F. (1966). Intestinal absorption of tracer quantities of chromium. *J. Lab. Clin. Med.* 68: 484-493.

El Masry, A.M., Smith, J.N., and Williams, R.T. (1956). Studies in detoxication 69. the metabolism of alkylbenzenes: n-propylbenzene and n-butylbenzene with further observations on ethylbenzene. *Biochem. J.* 64: 50-56.

EPA (1984). *Health Assessment Document for Chromium* (final report). August 1984. EPA 600/8-87-014F.

EPA (1985a). *Drinking Water Criteria Document for Chromium* (final draft). October 1985. PB86-118072.

EPA (1985b). *Health Advisories for 52 Chemical Which Have Been Detected in Drinking Water*. September 1985. PB86-118338.

EPA (1985c). *Drinking Water Criteria Document for Toluene*. March 1985. PB86-117975.

EPA (1985d). *Drinking Water Criteria Document for Xylenes* (final draft). March 1985. PB86-117942.

Fry, B.J., Taylor, T., and Hathaway, D.E. (1972). *Pulmonary elimination of chloroform and its metabolites in man*. Arch. int. Pharmacodyn. 196: 98-111.

Gomez, M.I.D., Swann, P.F., and Magee, P.N. (1977). The absorption and metabolism of small oral doses of dimethylnitrosamine. *Biochem. J.* 164: 497-500.

Hunter, C.G. (1966). Aromatic solvents. *Ann. Occup. Hyg.* 9: 193.

IARC (1982). IARC Monographs on the *Evaluation of Carcinogenic Risk of Chemicals to Man. Vols. 1 to 29, Supplement 4*. World Health Organization Publication, Geneva, Switzerland.

ICRP (1975). *Report of the Task Group on Reference Man*. ICRP Publication 23. Pergamon Press, New York.

ICRP (1980). *Limits for Intakes of Radionuclides by Workers*. ICRP Publication 30. Part 2. Pergamon Press, New York.

Junghans, R.P. (1983). A review of the toxicity of methylmercury compounds with application to occupational exposures associated with laboratory uses. *Environ. Research* 31: 1-31.

Kehoe, R.A. (1960). The metabolism of lead in man in health and disease. The Harben Lectures. *J. R. Inst. Public Health Hyg.* 24: 81.

Klaassen, C.D. (1980). Casarett and Doull's Toxicology. *The Basic Science of Poisons* (Doull, J., Klaassen, C.D., and Amdur, M., eds.), pp. 31-33. Macmillan Publishing Co., Inc., New York.

Kudsk, F.N. (1965). Absorption of mercury vapor from the respiratory tract in man. *Acta Pharmacol. et Toxicol.* 23: 250-262.

Lehmann, K.G. and Hasegawa (1910). Studies of the absorption of chlorinated hydrocarbons in animals and humans. *Arch. Hyg.* 72: 327-342.

Magee, P.N. (1956). Toxic liver injury. The metabolism of dimethylnitrosamine. *Biochem. J.* 64: 672-682.

McKenna, M.J., and Zempel, J.A. (1981). The dose-dependent metabolism of [$^{14}$C] methylene chloride following oral administration to rats. *Fd. Cosmet. Toxicol.* 19: 73-78.

Miettinen, J.K. (1973). Absorption and elimination of dietary mercury ($Hg^{2+}$) and methylmercury in man. In: *Mercury, Mercurials and Mercaptans* (Morton W. Miller and Thomas W. Clarkson, eds.), pp. 233-243. Charles C. Thomas, Springfield, Illinois.

NAS (1974). *Medical and Biological Effects of Environmental Pollutants. Chromium.* (Committee on Biologic Effects of Atmospheric Pollutants, National Research Council) Washington, D.C.

NAS (1975). *Nickel.* Committee on Medical and Biological Effects of Environmental Pollutants, Division of Medical Sciences, National Academy of Sciences, Washington, D.C. ISBN 0-309-02314-9.

Natusch, D.F.S. and Wallace, J.R. (1974). Urban aerosol toxicity: the influence of particle size. *Science* 186: 695.

Nomiyama, K., and Nomiyama, H. (1974). Respiratory retention, uptake, and excretion of organic solvents in man. *Int. Arch. Arbeitsmed.* 32: 85-91.

Nomiyama, K., and Nomiyama, H. (1978). Three fatal cases of thinner-sniffing, and experimental exposure to toluene in humans and animals. *Int. Arch. Occup. Environ. Hlth.* 41: 55-64.

NRC (1978). Chloroform, Carbon Tetrachloride and Other Halomethanes: An Environmental Assessment (NRC Panel on Low Molecular Weight Halogenated Hydrocarbons). National Academy of Sciences, Washington, D.C.

Parke, D.V., and Williams, R.T. (1953). Studies in toxication 49. The metabolism of benzene containing $^{14}C$-benzene. *Biochem. J.* 54: 231.

Rabinowitz, M.B., and Kopple, J.D. (1974). Lead metabolism in the normal human: stable isotope studies. *Science* 182: 725-727.

Rabinowitz, M.B., Wetherill, G. W. and Kopple, J.D. (1978). Magnitude of lead intake from respiration by normal man. *J. Lab. and Clin. Med.* 90: 238-248.

Rahola, T., Hattula, T., Korlainen, A., and Miettinen, J.K. (1971). The biological halftime of inorganic mercury ($Hg^{2+}$) in man. *Scand. J. Clin. Invest.* 27 (Suppl. 116): 77 (Abst.).

Sedivec, V., and Flek, J. (1976). The adsorption, metabolism and excretion of xylenes in man. *Int. Arch. Occup Environ. Hlth.* 37: 205-217.

Smith, J.N., Smithies, R.H., and Williams, R.T. (1954). Studies in detoxication 55. The metabolism of alkylbenzenes. *Biochem. J.* 56: 317.

Srbova, J., Teisinger, J., and Skramovsky, S. (1950). Absorption and elimination of inhaled benzene in man. *Arch. Ind. Hyg. and Occup. Med.* 2: 1.

WHO (1970). Fluorides and Human Health. World Health Organization Monograph Series No. 59. Geneva, Switzerland.

## INTERNAL DISTRIBUTION

1. J. S. Baldwin
2-3. L. W. Barnthouse
4. B. A. Berven
5. T. W. Burwinkle
6-8. K. W. Cook
9-13. C. E. Easterly
14. K. F. Eckerman
15. L. R. Glass
16. A. R. Hawthorne
17. D. D. Huff
18-27. T. D. Jones
28. D. C. Kocher
29. R. W. Leggett
30. L. E. McNeese
31. M. D. Morris
32-33. T. E. Myrick
34. C. E. Nix
35-36. B. A. Owen
37-51. P. T. Owen
52. F. E. Sharples
53. L. E. Stratton
54. J. R. Trabalka
55. L. D. Voorhees
56. P. J. Walsh
57. L. C. Waters
58. Laboratory Records-RC
59-60. Laboratory Records Department
61. Central Research Library
62. ORNL Y-12 Technical Library
63. ORNL Patent Section

## EXTERNAL DISTRIBUTION

64. Assistant Manager, Energy Research and Development, DOE-ORO, P.O. Box E, Oak Ridge, TN 37831
65-66. Office of Scientific and Technical Information, P.O. Box 62, Oak Ridge, TN 37831